

The American Heart Journal

VOL. 21

JUNE, 1941

No. 6

Original Communications

THE ASSOCIATION OF GALL BLADDER DISEASE AND OF PEPTIC ULCER WITH CORONARY DISEASE; A POST-MORTEM STUDY

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IT HAS long been known that a striking improvement in the symptoms of coronary insufficiency (angina pectoris) may follow the removal of a diseased gall bladder. Babcock¹ was among the first to recognize this apparent relationship, and he, among others,² believed that cholecystitis could in some instances even cause heart disease and, occasionally, congestive failure. Mayo and Straus and Hamburger³ have reported (and we too have observed) subsidence of certain cardiac arrhythmias after the removal or drainage of a troublesome gall bladder, and Osler⁴ was of the opinion that patients might die of cardiac standstill during severe biliary colic. Further evidence of the possible deleterious effects of disease of the gall bladder upon the function of the heart has been recorded electrocardiographically by Fitz-Hugh and Wolferth.⁵ In six patients with symptoms suggestive of coronary insufficiency and abnormal (inverted) T waves in the electrocardiogram, the removal of gall stones was followed by an improvement in the cardiac symptoms and a return of the T waves to the upright position. Also, certain experimental evidence bearing upon this apparent relationship has been presented by Buchbinder and others,⁶ who found that in icteric animals a reflex mechanism from distended biliary passages caused cardiac arrhythmias and heart block, probably by way of the vagus nerve.

Two years ago our interest in the relationship of gall bladder disease and also of peptic ulcer to disease of the coronary arteries was stimulated by the experimental work of Hall and his co-workers.⁷ In dogs they showed that the daily administration of acetylcholine frequently

Presented at the Sixteenth Annual Meeting of the American Heart Association, June 7, 1940.

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Received for publication June 24, 1940.

produced thrombosis of the coronary arteries which in many instances was associated with (1) abnormal thickening of the gall bladder and (2) ulcers in the stomach and small intestine. Furthermore, long continued electrical stimulation of the vagus nerve in their animals produced similar results.⁸ It was this experimental production of combined structural alterations in the coronary arteries, in the gall bladder, and in the gastrointestinal tract that caused us to re-examine the post-mortem records of the Massachusetts General Hospital for evidence of a comparable association in man, and to make a clinical survey of a large group of cases of coronary disease from this same standpoint.

In a clinical study of 1,000 patients with coronary disease, all of whom were seen in private consultation, we found clear evidence of gall bladder disease in sixty-eight (6.8 per cent), and of peptic ulcer in an additional twenty-seven (2.7 per cent); a state of vagotonia (as manifested chiefly by heart rate, A-V conduction time, and irritable gastrointestinal tract) was not preponderant in this series of 1,000 cases.

The protocols of 2,737 complete autopsies on persons 20 years, or more, of age, between Feb. 1, 1925, and Jan. 31, 1938, were examined. A simple classification of this material, as shown in Table I, seems the most satisfactory approach. There were 576 patients (21 per cent) with atherosclerosis of the coronary arteries of sufficient degree to be considered grossly abnormal. There were 456 patients (16 per cent) with structurally abnormal gall bladders. In 122 instances (4 per cent), both coronary disease and gall bladder disease were noted in the same person. Peptic ulcer occurred in 149 (5 per cent) of the total series of 2,737 cases.

A study of the significance of these data, with due consideration for the modifying effects of age and sex, is the basis of this report.

In analyzing our material we encountered a borderline group which was difficult to classify because of relatively slight, but abnormal, structural changes. We consider these minimal alterations in structure as of uncertain significance. Therefore, in the final analysis the chance of error is less if we confine our conclusions to a comparison of the definitely normal group, on the one hand, with the definitely abnormal group, on the other. For future reference, however, we have included in the tables, and designated as such, this intermediate borderline group.

The cases were classified as follows:

1a. No coronary disease.

1b. Coronary "disease" of *slight degree* was considered present in those with minimal atherosclerosis and without evident constriction of the arterial lumen. In this group the extent of atherosclerosis was too slight to be considered definitely significant, and hence these cases were set apart as a borderline group and labeled "minimal atherosclerosis."

TABLE I
POST-MORTEM OBSERVATIONS
(2,737 PATIENTS)

AGE	NORMAL CORONARY ARTERIES (1,222 CASES)				MINIMAL ATHEROSCLEROSIS (939 CASES)				CORONARY DISEASE (576 CASES)			
	20-39	40-59	60 PLUS	TOTAL	20-39	40-59	60 PLUS	TOTAL	20-39	40-59	60 PLUS	TOTAL
Normal gall bladder (2,193 cases)	397	497	161	1,055	68	310	334	712	5	124	297	426
Minimal cholesterosis (88 cases)	4	15	6	25	3	18	14	35	0	7	21	28
Gall bladder disease (456 cases)	26	78	38	142	6	73	113	192	1	23	98	122

1c. Coronary disease of *moderate to marked* degree was considered present in those with well-advanced atherosclerosis and demonstrable narrowing of the arterial lumen; the latter varied in degree from slight constriction to complete occlusion. Approximately 10 per cent were also included here because of extreme sclerosis and rigidity of the vessel wall, even though actual constriction was not recognized. More than half had calcium deposits in the vessel walls. This represents the group designated "coronary disease," and used in this report for a comparison with the strictly normal group.

2a. No gall bladder disease.

2b. Gall bladder "disease" of *slight degree* included those who showed, post mortem, slight or even moderate cholesterosis, but no stones. Alteration of this degree was held by us to be of uncertain significance, and hence was set apart with the designation "minimal cholesterosis." This group was not considered in the final comparison.

2c. Gall bladder disease of *moderate to marked* degree included those with or without an abnormally thickened gall bladder which contained one or more stones. Approximately 5 per cent were included because of extreme thickening of the wall, even though stones were absent. Whether or not one is justified in considering the presence of stones, per se, as always indicating gall bladder disease is open to question. However, there appeared to be less chance of error in arbitrarily including all, rather than attempting to exclude some. In twenty instances (4 per cent), cholecystectomy had been performed. These were included in the belief that the operation had been indicated. This then represents the group (456 in number) which we have called "gall bladder disease."

3. *Peptic ulcer* offered less difficulty in classification. It was considered to have been present in all who had evidence of either an active or a well-healed lesion in the stomach or duodenum. None was of the agonal (terminal) type.

DISEASE OF THE GALL BLADDER AND CORONARY ARTERIES

In the group of 576 patients with coronary disease, the added complication of gall bladder disease occurred in 122, or 21 per cent (Table I), whereas, in the 1,222 patients with normal coronary arteries, gall bladder disease was noted in only 142, or 11.5 per cent. Furthermore, this apparently significant association is still evident if we consider (from a slightly different approach) the incidence of coronary disease in the total group with gall bladder disease, since this includes 192 additional instances of gall bladder disease which were noted in those with "minimal atherosclerosis," and hence were not considered in the first comparison. Thus, the gall bladder disease which was present in a total of 456 cases was complicated by coronary disease in 122, or 27 per cent, in contrast to an incidence of 19 per cent in those without gall bladder disease (426 in a total of 2,193 cases).

These rather broad comparisons suggest a slight, but apparently significant, tendency for gall bladder disease and coronary disease to occur in the same person. However, the possibility that certain modifying factors, such as age and sex, may have distorted our analysis warranted further scrutiny.

When one compares this association in males and in females the same general trend is still evident. As shown in Table II, there were 415 men with coronary disease, sixty-nine of whom had abnormal gall bladders (16 per cent), in contrast to an incidence of 8 per cent (sixty-one instances) of abnormal gall bladders in the 710 men with normal coronary arteries. A similar comparison among the women indicates that, of the 161 with coronary disease, fifty-three (33 per cent) also had abnormal gall bladders and, of the 512 women with normal coronary arteries, only eighty-one (16 per cent) had gall bladder disease.

In accord with clinical observation, gall bladder disease occurred in this post-mortem study more often in women (22 per cent) than in men (12 per cent), and, as was also to be expected, the reverse was true with regard to the incidence of coronary disease, which was present in 37 per cent of the males as compared to 24 per cent of the females, excluding the intermediate group with minimal atheroma.

It is interesting to observe that, in spite of this apparent tendency for the two conditions to occur in the same person, in those under the age of 40 (Table I) there was less of an association than in the group as a whole and there was a considerable increase in both with each successive decade. Statistical tests made by Dr. E. B. Wilson, of the Department of Statistics, School of Public Health, Harvard University, have confirmed the impression that the increasing incidence of gall bladder disease and of coronary disease after 20 years of age did not surpass the increment expected with mounting numbers in each group. The coincidence of the two conditions in the same individuals is, however, not to be accounted for by age alone; there remain some factor or factors that need further elucidation.

PEPTIC ULCER AND CORONARY DISEASE

Peptic ulcer was found in a total of 149 instances in this post-mortem series, an incidence of 5 per cent. Well-marked coronary disease was a complication in thirty patients (20 per cent), whereas sixty-eight (45 per cent) had entirely normal coronary arteries. This same incidence of coronary disease was noted in the remaining 2,588 patients without peptic ulcer; 546 (21 per cent) had definite coronary disease and 1,154 (45 per cent) had none. This apparently negative relationship between peptic ulcer and coronary atherosclerosis is further illustrated in Table III. Here it is apparent that peptic ulcer occurred in thirty (5 per cent) of the 576 patients with coronary disease, and with equal frequency (sixty-eight, or 5.5 per cent) among 1,222 patients

TABLE II
RELATION TO SEX AND AGE

AGE	NORMAL CORONARY ARTERIES (1,222 CASES)				MINIMAL ATHEROSCLEROSIS (939 CASES)				CORONARY DISEASE (576 CASES)			
	20-39	40-59	60 PLUS	TOTAL	20-39	40-59	60 PLUS	TOTAL	20-39	40-59	60 PLUS	TOTAL
<i>Males (1,757 Cases)</i>												
Normal gall bladder (1,481 cases)	221	300	117	638	52	224	241	517	5	104	217	326
Minimal cholesterosis (49 cases)	1	7	3	11	1	9	8	18	0	4	16	20
Gall bladder disease (227 cases)	11	30	20	61	1	36	60	97	0	15	54	69
<i>Females (980 Cases)</i>												
Normal gall bladder (712 cases)	176	197	44	417	16	86	93	195	0	20	80	100
Minimal cholesterosis (39 cases)	3	8	3	14	2	9	6	17	0	3	5	8
Gall bladder disease (229 cases)	15	48	18	81	5	37	53	95	1	8	44	53

TABLE III
PEPTIC ULCER

AGE	NORMAL CORONARY ARTERIES (1,222 CASES)				MINIMAL ATHEROSCLEROSIS (939 CASES)				CORONARY DISEASE (576 CASES)			
	20-39	40-59	60 PLUS	TOTAL	20-39	40-59	60 PLUS	TOTAL	20-39	40-59	60 PLUS	TOTAL
<i>Males (1,757 Cases)</i>												
Peptic ulcer (118 cases)	8	32	11	51	4	19	16	39	1	9	18	28
No ulcer (1,639 cases)	226	304	129	659	50	250	293	593	4	114	269	387
<i>Females (980 Cases)</i>												
Peptic ulcer (31 cases)	4	13	0	17	0	4	8	12	0	1	1	2
No ulcer (949 cases)	190	240	65	495	23	128	144	295	1	30	128	159

without coronary disease. The majority, fifty-one of the eighty-one patients with peptic ulcer (63 per cent), had the least coronary disease, which, in turn, emphasizes further the lack of association between ulcer and coronary heart disease. In accord with clinical experience, most of the ulcers were in men (118). Since the proportion of males to females in the total series was 1,757 to 980, the relative frequency of ulcer in men as compared to women in this series was approximately 2 to 1.

DISCUSSION

The results of this study, supported by statistical tests, are in agreement with those of previous workers⁹ who have failed to find evidence from post-mortem investigation that diseases of the gall bladder and of the coronary arteries are closely related except through the occurrence of an unknown "aging" factor.

Clinical experience, however, indicates that a troublesome gall bladder or peptic ulcer may seriously disturb cardiac function in the presence of otherwise silent coronary disease. Disturbed functions in other organs may also act in the same way, but disease of the upper gastrointestinal tract and of the gall bladder appears to have a more profound effect, probably because of the proximity of the respective nerve pathways in the spinal cord and of related activities of vagal reflexes.

We have been unable to assemble evidence from this post-mortem survey to suggest the occurrence in man of a close association between disease of the gall bladder and upper intestinal tract and disease of the coronary arteries which is comparable in any degree to the important structural alterations produced experimentally in dogs by acetylcholine or through vagal stimulation.

Since the completion of this report, Breyfogle¹⁰ has published the results of his studies concerning the coexistence of gall bladder and coronary artery disease. In a series of 1,493 autopsies he found an even more positive association than ours between disease of the gall bladder and that of the coronary arteries. The differences between his findings and ours are to be accounted for, in large part at least, by the higher proportion of young persons and of women in his group.

CONCLUSIONS

From a study of the records of 2,737 post-mortem examinations of adult patients, it has been shown that:

1. Gall bladder disease occurred almost twice as often in patients with coronary disease as in those with normal coronary arteries. Some factor or factors related, in part at least, to an aging process but as yet not definitely elucidated are apparently responsible for this finding.
2. There was no indication of a significant association of peptic ulcer and coronary disease in the same person.

3. In contrast to the important structural alterations simultaneously produced experimentally in the gall bladder, in the upper intestinal tract, and in the coronary arteries of animals, as previously reported, no conclusive evidence of a comparable association in man was apparent from the present study.

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DISCUSSION

DR. PAUL D. WHITE, Boston.—I would like to emphasize very briefly two important points in this study of the correlation or association of gall bladder disease and coronary disease. The first concerns the low incidence of both conditions together in the younger patients. For example, of twenty-seven patients with severe gall bladder disease under the age of 40, twenty-six had normal coronary arteries; only one had coronary disease of moment; whereas, of six patients with coronary disease of considerable moment under the age of 40, five had normal gall bladders and only one had gall bladder disease.

The second point concerns the greater frequency with which gall bladder disease is found in women than in men, and the greater frequency of coronary disease in men than in women at earlier ages.

These facts indicate that whatever mechanism is producing coronary disease in young people is not at the same time producing gall bladder disease, and vice versa.

DR. ERNST P. BOAS, New York.—This valuable study has interested me in particular because for some years Dr. Hyman Levy and I have devoted some attention to the association of peptic ulcer and coronary disease. At first we had the impression that these two conditions frequently occurred together, but a more complete review of our clinical material gives results corresponding to those of Dr. Walsh, Dr. Bland, and Dr. White.

However, there are certain phenomena which suggest that in individual cases there is a causal relationship between these two conditions. I refer to cases, which are not so very rare, in which coronary thrombosis and an acute, penetrating, peptic ulcer apparently occur simultaneously. I have seen a number of such cases in which the diagnosis of cardiac infarction was confirmed by the electrocardiogram and the penetrating ulcer was demonstrated roentgenologically, in which the symptoms of the two conditions were difficult to distinguish from one another. Here I am not referring to the well-known cardiac infarction that occurs as a result of severe hemorrhage from an ulcer, but to cases in which there was a simultaneous onset of pain in the epigastrium and in the chest with various types of radiation.

Second, there are patients with angina pectoris who have or develop peptic ulcer, in whom the anginal pain develops an ulcer timing. Instead of having the anginal pain predominantly on exertion, these patients are likely to get the anginal pain an hour or so after meals, and are frequently relieved by alkalies.

The analysis of this clinical picture is difficult because of the cross radiation of pain when these two conditions are associated, and because the respective symptoms become so closely intermixed. For instance, if a patient first has a peptic ulcer and then develops angina pectoris, he may have typical anginal pain on exertion, and then, when he gets his ulcer pain after eating, it will be felt in the precordium instead of in the epigastrium and will radiate down the left arm.

I fully realize that these scattered observations do not represent a tremendous mass of material nor prove any definite etiological relationship between the two conditions. However, we must keep in mind that cardiac infarction may arise through different types of pathologic processes and that it is quite conceivable that in certain instances the same arterial disease or the same arterial insult may manifest itself simultaneously in a coronary artery and in a gastric artery.

We concede that gall bladder disease and coronary disease are not frequently related, yet in cases such as those described by Fitz-Hugh and Wolferth there seems to have been a very direct relationship.

Although the statistical analysis made in this paper disproves a direct relationship between peptic ulcer, gall bladder disease, and coronary disease in the majority of instances, we must not conclude that there is never any relationship, but recognize that further intensive study may bring out common factors in some of these cases which so far have escaped recognition.

A COMMON ELECTROCARDIOGRAPHIC VARIANT FOLLOWING ACUTE MYOCARDIAL INFARCTION—THE T_N TYPE

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IT HAS now been definitely established by careful correlation of clinical, electrocardiographic, and anatomical findings that acute myocardial infarctions produce a series of changes in the contour of the electrocardiogram, in a large percentage of cases, which are helpful in diagnosis. Soon after Herrick¹ called attention to the clinical picture of coronary thrombosis, Smith² described the electrocardiographic changes found in acute myocardial infarction in the experimental animal, and Pardee³ those in a patient. Since then a large and well-founded literature on this subject has appeared.⁴⁻¹⁸ Parkinson and Bedford⁴ first pointed out two particularly characteristic patterns which may occur: The T_1 type, in which the T wave in Lead I becomes inverted, and the T_3 type, in which the T wave in Lead III becomes inverted; classically the S-T segment and T wave of Leads I and III present a reciprocal appearance as far as direction is concerned. Wilson and his co-workers⁵ indicated that changes in the initial ventricular deflection are also common, a Q pattern tending to appear in the same lead in which the T wave becomes inverted. Barnes and Whitten⁶ attempted to correlate the electrocardiographic pattern with the location of the infarction as demonstrated at autopsy; they found that the Q_1T_1 type occurred when the anterior surface of the left ventricle was infarcted, and the Q_3T_3 type when the posterior surface of the left ventricle was thus involved.

These fundamental contributions have gained general acceptance, and are quoted in most textbooks on electrocardiography. It is unfortunate, however, that too often they have been stressed as being the sole criteria for the electrocardiographic diagnosis of acute myocardial infarction. Unless the above criteria are amplified, the electrocardiograph becomes an inefficient diagnostic instrument, and may even conceivably become a dangerous one. Four additional considerations must be taken into account; they are: (1) The electrocardiogram following an acute myocardial infarction has as a major characteristic a tendency to change serially over a relatively short period, i.e., over the course of days or weeks. (2) The chest leads may bring out evidence of this condition, not uncommonly in the absence of diagnostic limb lead changes. (3) The entire record may show either non-diagnostic or, for a time at least, no changes following an acute myo-

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Aided by the A. D. Nast Fund for Cardiac Research and the A. B. Kuppenheimer Fund.

Received for publication June 24, 1940.

cardial infarction, and (4) The changes in the electrocardiogram after acute myocardial infarction may follow a pattern which differs from those widely accepted as classical. The first two considerations have already received extensive attention in the literature,^{7-10, 11-14} and the third might well deserve it.¹⁵⁻¹⁸ It is with the fourth, however, that this communication is concerned.

In this Heart Station we have found it to be the exception rather than the rule for serial records following coronary occlusions to show the pure, classical Q_1T_1 or Q_3T_3 changes. Among the many records which stray from the typical, we have been struck by the frequency of a pattern which deserves greater mention than it has hitherto received. This group of cases is characterized by the occurrence, at some time or another during the evolution of the electrocardiogram following acute myocardial infarction, of T waves which are simultaneously inverted in all three of the standard limb leads. Because the T wave in all three leads is negatively directed, we call this the T_N pattern¹⁹ to conform with the nomenclature in common use. In this communication all the T_N records in recent myocardial infarctions in our files are assembled for analysis.

SELECTION OF CASES

The records of all cases listed under "acute myocardial infarction" in the Heart Station files since 1930 were examined. Of this group those cases which showed an inverted T wave in all three limb leads at some stage in their evolution were chosen for this study. The clinical histories of the latter were then collected and correlated with the electrocardiographic records. Those cases in which the electrocardiographic evolution and/or the clinical evidence indicated beyond reasonable doubt that an acute or healing myocardial infarction was present were selected for this presentation; the others were discarded.

Our criterion for T wave negativity was simply that the T waves be inverted; no particular configuration was demanded. In many cases the inverted T waves were of the so-called "coronary" contour in all three leads (Figs. 5, 7), in some cases only in one or two of the leads (Fig. 4), and rarely in none (Fig. 1).

OBSERVATIONS

Out of a total of 743 cases of myocardial infarction listed in our files since 1930, sixty showed a T_N pattern at some time or another during the electrocardiographic evolution, an incidence of 8.1 per cent. However, we adopt a very conservative attitude and suggest the diagnosis of recent coronary occlusion whenever the electrocardiogram is even slightly suspicious, and such a record is automatically indexed in the files as an infarction. Further study often disproves the diagnosis, but the initial indexing is not cancelled. Analysis indicated that only 380 of the 743 cases conformed to the same criteria which we set

up for the 60 records accepted for this report. Using the corrected figures we found that 15.8 per cent of the cases proved beyond reasonable doubt to be acute myocardial infarctions showed a T_N pattern at some stage during their electrocardiographic evolution. We realize that the pattern we are describing represents a purely artificial classification, and that an accurate statistical analysis, therefore, has no particular significance. The above figures are quoted only to bring out the fact that the T_N type is a not infrequent occurrence.

The age of the patients varied from 34 to 77, the average age being 57.2 and the mean age 58. Forty-four of the patients were males and 16 females. Seven of the 60 patients came to autopsy. Three of these have been previously illustrated in the literature. The records of three of the other four cases are shown in Figs. 1-3, and the data on all seven are summarized in Table I.

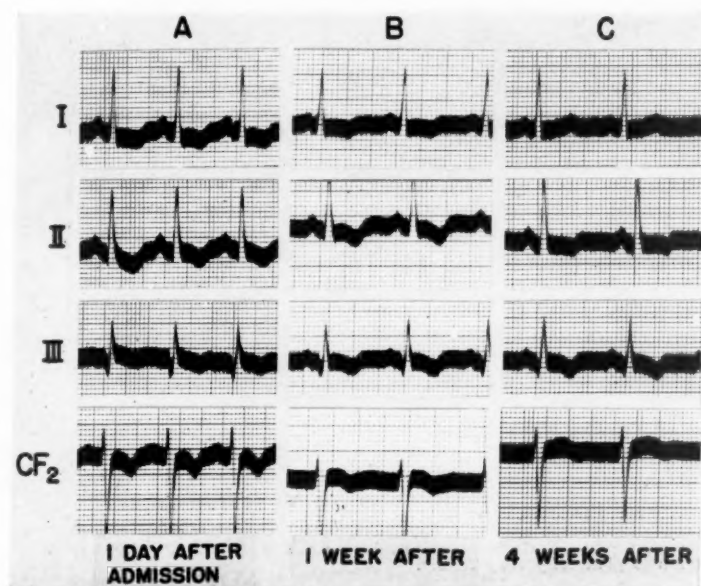


Fig. 1.—This patient, a female, aged 40, entered the hospital with a history of substernal pain for four weeks, especially severe the latter two weeks, and not relieved by nitroglycerin. The changes between the first two records, both of which may be classed as T_N , suggest that an infarct had occurred. The diagnosis is confirmed by the changes seen in record C. The patient re-entered the hospital eight months later in a comatose condition and died within 24 hours. At post-mortem examination there were found, in addition to a recent infarction of the left ventricle, two healed infarcts. One, measuring 9 cm. in diameter, involved the septum and posterior wall of the left ventricle, the other, in the anterior apical region, measured 1.5 cm. The most probable explanation for the T_N pattern in this case is that the anterior wall infarction was in the healing stage at the time of the first hospitalization, while the posterior wall infarct had been present previously, as indicated by the persistent Q_3T_3 . The combination produced inverted T waves in all three limb leads.

These sixty cases constitute a heterogeneous group. In some the T_N character appeared at the onset (Fig. 3), in others at a later stage in healing (Fig. 5). In some this represented a transitory finding (Fig. 4), in others it was more protracted (Fig. 7). In many of the records we could identify a pattern which permitted us to presumptively localize

the infarction. This may have been done through the presence of a particular Q pattern (Fig. 5), through the appearance of the chest leads (Fig. 4), or through the development, either before or after the T_N stage, of a characteristic T_1 or T_3 type (Fig. 7). In many records, however, we were unable to do so, because evidence was either lacking or conflicting (Fig. 2).

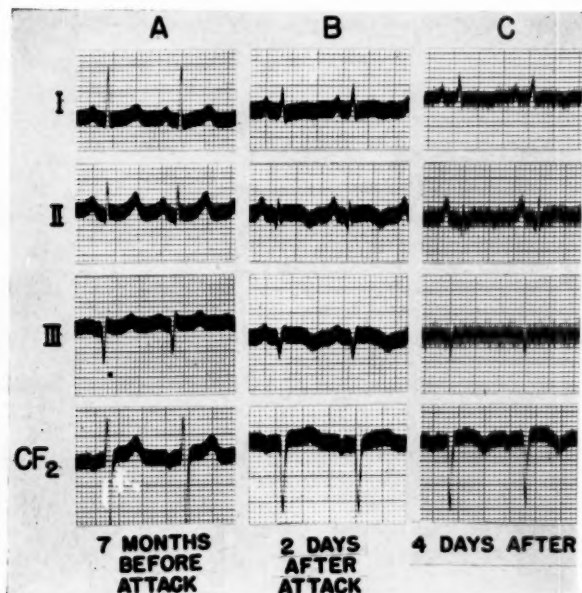


Fig. 2.—This patient, a female, aged 50, entered the hospital, one hour after an attack of severe epigastric pain. The record taken 2 days later, showing a T_N pattern, indicated that an acute myocardial infarction had occurred, and the last record (deformed by a 60 cycle artefact) confirmed the diagnosis. The patient died six days later. At post-mortem examination a recent infarct of the posterolateral wall of the right ventricle and posterior portion of the interventricular septum was found, and also an old healed infarct of the anterior apical portion of the left ventricle. No evidence of pericarditis was seen. There are two possible explanations for the T_N pattern in this case. One is the atypical location of the acute infarct, i.e., in the right ventricle. The second is the involvement of both posterior and anterior walls. The changes seen in Lead CF_2 support the latter concept, even though anatomically only an old infarction was found anteriorly. However, we are unable to say which of the two mechanisms is primarily responsible.

DISCUSSION

We subjected all the T_N cases to close study in an attempt to explain the reason for its occurrence, and discovered that there are at least seven possible mechanisms which may be responsible.

1. Acute infarction may involve both the anterior and posterior walls of the left ventricle either by separate involvement of these two areas, or by a massive infarction which involves both together by confluence or extension. In either case there is a tendency for both T_1 and T_3 types to develop, so that the composite may show any combination of these two types. Under fortuitous circumstances a T_N type may result (Fig. 3).

2. Acute infarction may occur in the presence of pre-existing coronary insufficiency, either with or without a previous infarction. Recent investigations^{20, 21} strongly suggest that a relatively sudden occlusion in one coronary artery could produce ischemia in one area to the point of infarction, while producing a lesser degree of ischemia in another area not adjacent. From the latter, injury currents may arise, even in the absence of anatomical evidence of infarction,²² and summate with those from the acutely infarcted area to produce a T_N pattern (Fig. 1).

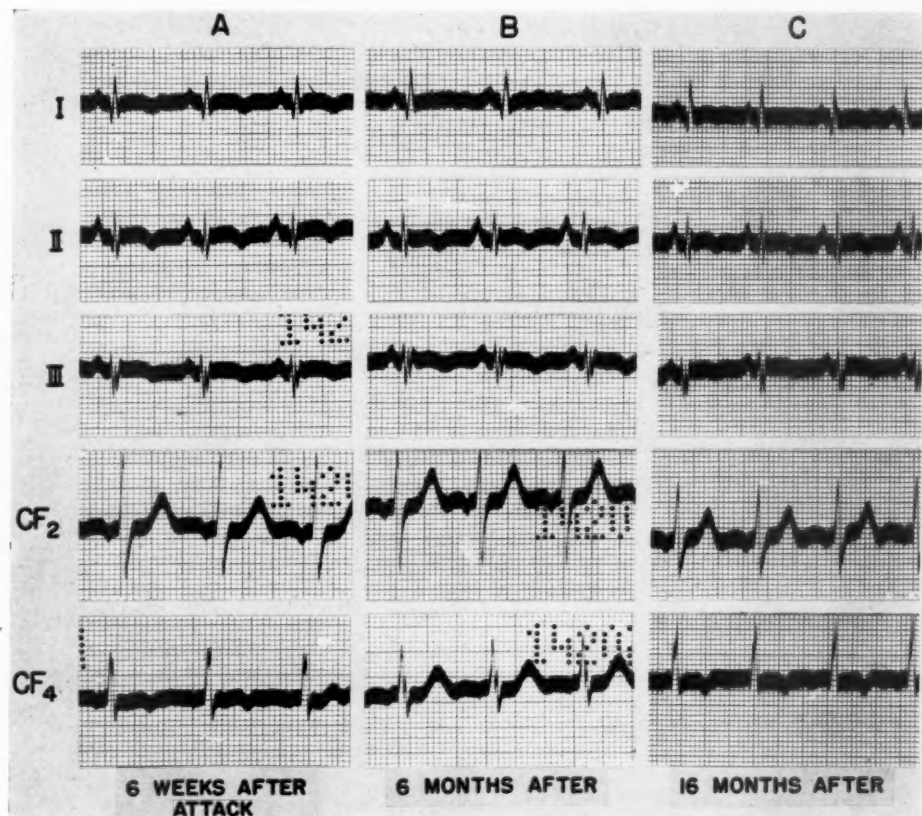


Fig. 3.—This patient, a female, aged 50, had an attack clinically diagnosed as an acute coronary occlusion and had been kept at home in bed for six weeks before the first electrocardiogram. The third record was taken when she entered the hospital for an unrelated surgical condition, of which she died one week later. At post-mortem examination a healed infarct was found, involving the apex, lateral wall, and posterior surface of the left ventricle. On the posterior surface, the wall was thinned out over an area approximately 2 cm. in diameter, and overlying this was a patch of adherent pericardium. In this instance the simultaneous involvement of two surfaces produced a T_N pattern.

3. Pericarditis may by itself affect the electrocardiogram to the point of producing inverted T waves of the so-called "coronary" contour in all three limb leads.²³⁻²⁵ When complicating an acute myocardial infarction, therefore, diffuse pericarditis may produce a

T_X pattern (Fig. 5). When localized to the area of infarction, however, pericarditis should not disturb the pattern produced by the infarct itself.²⁶

4. An acute posterior wall infarction of the T_3 type may occur in a patient whose electrocardiogram previously showed evidence of preponderant hypertrophy of the left ventricle in which $S-T_1$ is depressed and T_1 inverted. In such a case T_1 may remain inverted, and, when T_2 and T_3 become inverted, a T_X pattern results (Fig. 6).

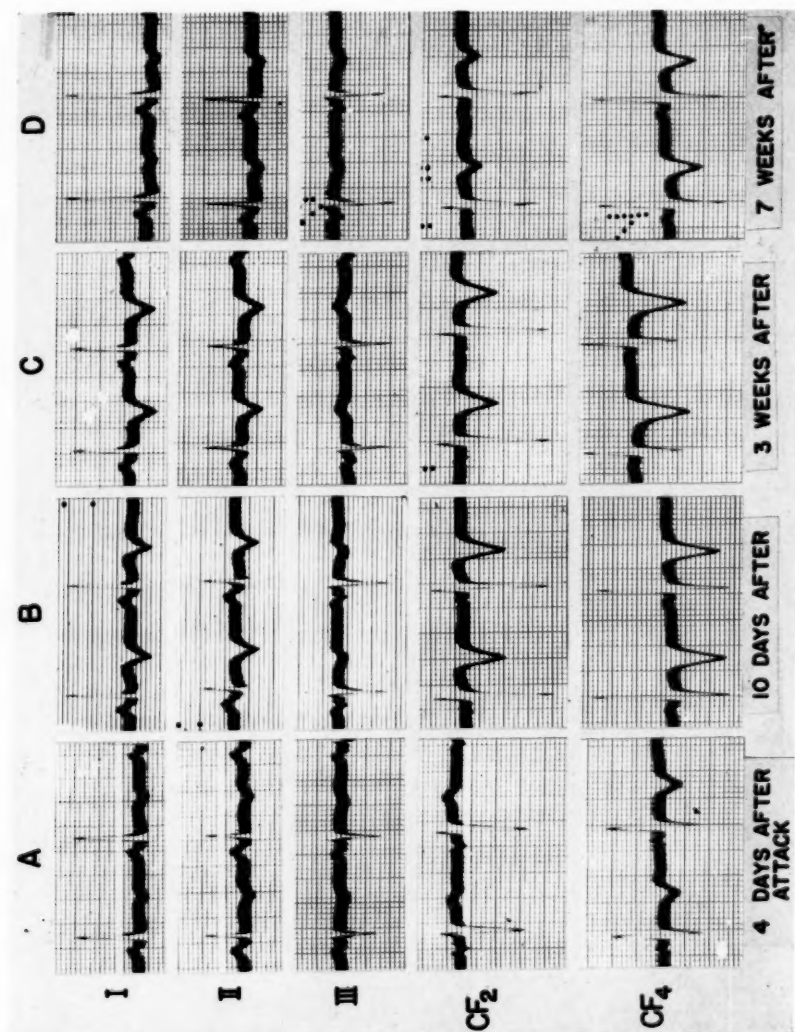


Fig. 4.—This patient, a female, aged 73, entered the hospital three days after an attack of precordial pain of one-half hour's duration, not relieved by nitroglycerin. The electrocardiographic evolution indicated the presence of an acute anterior wall infarction. Apparently T_3 was inverted at the outset; it was not until the third record that the reciprocal character of Leads I and III appeared, and later, T_3 again became inverted. The T_3 inversion in this case was probably a normal or incidental occurrence, and explains the T_X pattern.

5. An acute anterior wall infarction of the T_1 type may occur in a patient whose electrocardiogram previously showed an inversion of T_3 . This T_3 inversion may be a normal finding, may be associated with a right ventricular preponderance, or may be the residual of an old T_3

(posterior wall) type of infarction; in the latter instance it could also fall into Group 2 above. In any case, T_s may remain inverted, and, when T_1 and T_2 become inverted, a T_N pattern results (Fig. 4).

6. An acute infarction may be located elsewhere than in the areas particularly favorable for the production of the pure T_1 or T_s type. Under fortuitous circumstances this may produce the T_N pattern. Among the possible atypical locations are the lateral surface of the left ventricle and any portion of the right ventricle (Fig. 2).

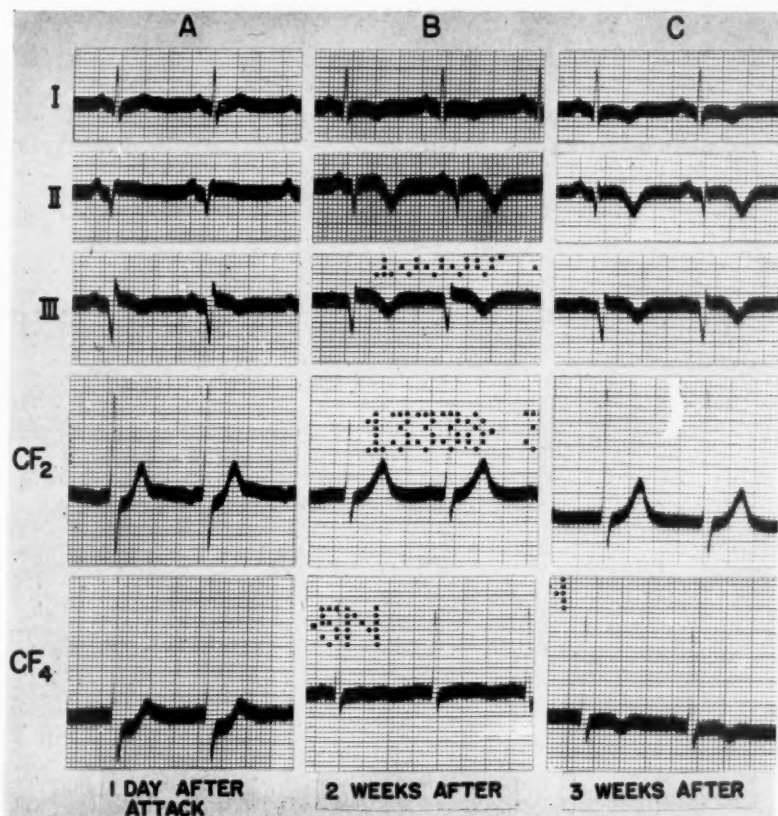


Fig. 5.—This patient, a male, aged 65, entered the hospital complaining of severe chest pain of twelve hours' duration. The first electrocardiogram showed changes typical of a posterior wall infarction. On the third hospital day a pericardial friction rub was heard. Since the infarct was located on the posterior wall of the heart, elicitation of a friction rub suggested that a diffuse, rather than localized, pericarditis was present. This would account for the T_N pattern seen in the next two records, and also for the changes seen in Lead CF_4 .

7. When intraventricular block is present, the final, as well as the initial, ventricular deflection is usually abnormal in contour. This may influence the electrocardiographic pattern to such an extent that a T_N type will occur following an acute myocardial infarction.

It is possible that other mechanisms may be involved; three that may be mentioned are: (1) Digitalis administration²⁷ (2) rotation of the

heart on its long axis accompanying dilatation²⁸ (3) infarction predominantly involving certain muscle bundles, and (4) pulmonary embolism complicating an anterior wall infarction.²⁹ However, we were unable to connect any cases in our series with these latter mechanisms.

The anatomic findings in the autopsy cases of our series are presented in Table I, and in the cases collected from the English literature in Table II; in each instance an attempt is made to explain the cause of the T_N pattern from the data available. These cases may not represent an accurate cross-section from which the relative frequency of the various mechanisms can be determined, because those patients that die might be expected to show multiple infarctions, and therefore no conclusions on this matter are drawn. In those patients of our series who did not come to autopsy only a few presented clear-cut evidence that one of the above-mentioned mechanisms was operating; in many instances a satisfactory conclusion could not be reached. The latter

TABLE I

AUTHORS		AUTOPSY FINDINGS	EXPLANATION FOR T_N PATTERN
Saphir, Priest, Hamburger, and Katz ²⁰	Fig. 26	Anterior apical infarction with circumscribed local pericarditis.	No explanation.*
	Fig. 30	Myocardial infarctions with aneurysmal dilatation of apex and posterior wall of the left ventricle.	(1) More than one region involved. (2) Presence of intraventricular block.
Bohning and Katz ¹⁰	Fig. 6B	Healed infarcts of posterior wall of left ventricle and anterior wall of left ventricle. Organizing infarct of apex of left ventricle.	More than one region involved.
This report	Fig. 1	Old infarcts in posterior wall of left ventricle and septum and in anterior apical region.†	More than one region involved.
	Fig. 2	Recent infarct of posterolateral wall of right ventricle and posterior portion of the intraventricular septum. Old infarct of the anterior apical portion of left ventricle.	(1) Atypical location—right ventricle. (2) More than one region involved.
	Fig. 3	Healed infarct involving anterior, lateral, and posterior surfaces of left ventricle. Localized pericarditis over posterior portion of the above infarct.	More than one region involved.*
	Not illustrated	Old infarct involving septum (not further specified).‡	No explanation.‡

*A circumscribed local pericarditis should produce no changes in the electrocardiogram to disturb the pattern produced by the myocardial infarction underlying it.²⁰

†Patient died of a recurrent myocardial infarction, evidence of which was also seen at necropsy.

‡In this case nothing found at necropsy could be used as a valid explanation.

may have been due to the fact that more than one possibility was discernible or to the fact that no clear evidence could be found. To illustrate some of the varieties which were encountered, seven typical

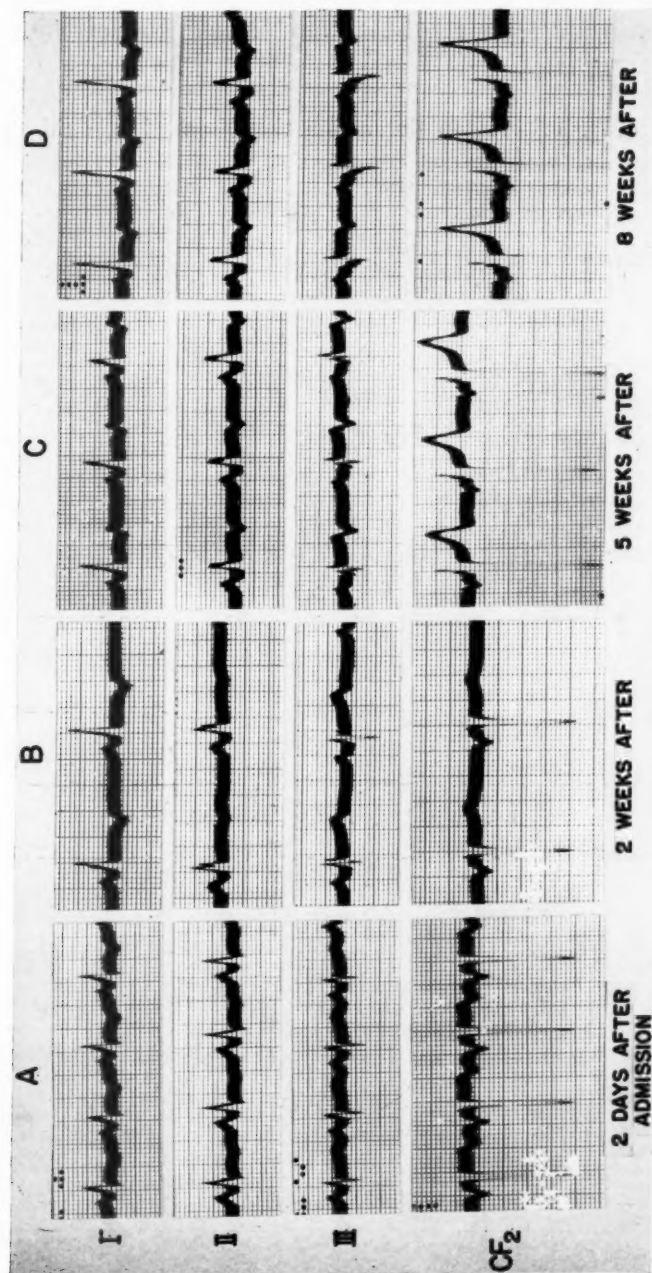


Fig. 6.—This patient, a colored male, aged 54, entered the hospital complaining of hemoptysis of one day's duration. A diagnosis of pulmonary infarction was made. He had been known to have arterial hypertension (186/110 mm. Hg) for at least two years, but denied having had any chest pain. His course in the hospital was entirely uneventful, but serial electrocardiograms revealed changes during the latter weeks typical of those seen in the healing of recent infarcts of the posterior wall of the left ventricle. Superimposed upon a record indicating left ventricular preponderance in that S-T₁ is depressed and T₁ inverted, at one stage (D) a T_N pattern developed, although at an earlier stage (C) T₁ had become biphasic. Although post-mortem confirmation was not available, the electrocardiographic evidence in this case is definite enough to suggest a diagnosis of a "silent" myocardial infarction.

records from our series are shown in Figs. 1-7, together with a short discussion in the legend of the factors which may have operated in each case to produce the T_N pattern.

The primary purpose of this communication is to point out that the electrocardiogram following acute myocardial infarction may not infrequently show inverted T waves in all three limb leads instead of the so-called "classical" picture of reciprocal appearance of the T waves in Leads I and III. When the T waves are found inverted in both these leads, therefore, a recent myocardial infarction should be considered, and other criteria to determine the diagnosis should be utilized.

TABLE II

AUTHORS	AUTOPSY FINDINGS		EXPLANATION FOR T _N PATTERN
Willius and Barnes ³⁰	Fig. 1	Recent infarcts of upper half of intraventricular septum and of posterior basal surface of left ventricle, each 2 cm. in diameter. Organized mural thrombus at apex.	(1) Posterior wall (T ₃) type of infarct superimposed on a previous left ventricular preponderance.* (2) More than one region involved.†
	Fig. 18	Recent infarct of anterior wall of left ventricle and old healed infarct of posterior portion of left ventricular septum.	(1) More than one region involved. (2) Presence of intraventricular block.
Levine ³¹	Fig. 27	Infarction of left ventricle at apex extending over posterior surface.	More than one region involved.
	Fig. 40	Obliterated pericardial sac, aneurysm of apical portion of left ventricle with mural thrombus.	Pericarditis.
	Fig. 79	Infarct of left ventricle with mural thrombus (not further specified).	No explanation.‡
Winternitz ³²	Fig. 2	Aneurysm involving wall of the left ventricle, septum, and apex.	More than one region involved.
Barnes ³³	Fig. 1	Anterior infarction with adherent pericarditis involving all but the posterior wall of the left ventricle.	Pericarditis.
Wood, Wolferth and Bellet ³⁴	Fig. 6	Massive infarction of posterior and lateral walls and posterior portion of septum. Also large healed infarct of anterior wall.	(1) More than one region involved: (a) Massive acute infarction. (b) Recent infarction in presence of old infarction. (2) Posterior wall (T ₃) type of infarct superimposed on a previous left ventricular preponderance.
Pardee ³⁵	Fig. 34	Lateral wall infarct.	Atypical location.

*Patient was known to have had hypertension, and the electrocardiogram is compatible with the pattern of left ventricular preponderance.

†Presence of organized mural thrombus is presumptive evidence of previous infarction in myocardium overlying it.

‡This patient had an atypical clinical attack. Nothing in the electrocardiographic tracing nor in the report of autopsy findings satisfactorily explains the occurrence of the T_N pattern.

Secondarily, we have presented seven different mechanisms which, acting either singly or in combination, may produce the T_N pattern.

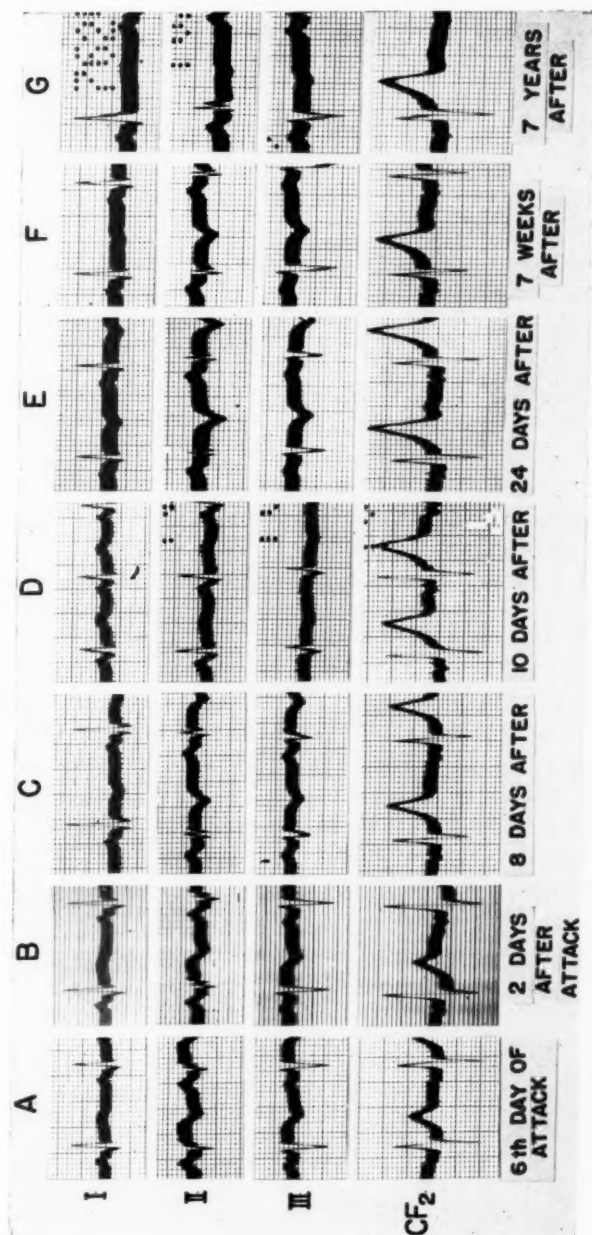


Fig. 7.—This patient, a male, aged 58, entered the hospital complaining of severe pain in the right parasternal area of five days' duration. Although no evidence of pericarditis was elicited clinically, the evolution in the first three electrocardiograms is typical for that seen in cases of acute posterior wall infarctions complicated by diffuse pericarditis. However, we are not aware of evidence indicating that the phenomenon seen in record D, i.e., temporary reversal of an inverted T wave to upright, is characteristic of the electrocardiographic evolution in pericarditis. An alternative explanation would assume that anterior wall involvement was present in addition to that on the posterior surface. The persistent Q_i tendency lends support to this possibility, and in the healing stages of myocardial infarctions we have seen transitory reversals in the direction of the T wave.²⁸

Barnes³³ has suggested that the diagnosis of pericarditis complicating infarction could be made when this electrocardiographic picture was seen. However, examination of the autopsy cases in Tables I and II

shows that in twelve of the sixteen no evidence of pericarditis was described at post-mortem examination. This lends weight to our interpretation of the multiple mechanisms involved in those patients of our series who did not come to autopsy (Figs. 4-7). Our analysis does not favor the view that all instances of the T_N contour are due to diffuse pericarditis.

It is obviously important to differentiate these cases from those of pericarditis without infarction, in which inverted T waves in the three limb leads are also found. Other criteria, especially the QRS pattern, the contour of the chest leads, and/or the evolutionary changes together with the clinical history and findings are important in making this differential diagnosis.^{36, 37}

In discussing the T_N pattern we lay claim neither to prior discovery nor to unusual observation. Perusal of the literature reveals that as early as 1925 Willius and Barnes³⁰ pointed out that 5 of their 9 patients with coronary occlusion showed inverted T waves in all three limb leads and that the same phenomenon could be seen in other isolated instances. All cardiographers have undoubtedly seen such in their own experience. The greater incidence in our series than its general occurrence in the collected literature is perhaps due to our insistence, when feasible, on frequent electrocardiographic records on all recent myocardial infarcts, since many times the T_N pattern is present only for a short time.

SUMMARY AND CONCLUSIONS

1. In sixty cases from the files of the Heart Station in the last ten years there were simultaneously inverted T waves in all three limb leads at some stage in the evolution of the electrocardiogram following acute myocardial infarction. This pattern is called the T_N pattern to conform with the nomenclature in common use.

2. Seven different mechanisms are presented as being possible factors in the production of this pattern and four further ones are suggested.

3. The importance of realizing that the T waves following acute myocardial infarction may be inverted in both Lead I and Lead III instead of presenting a reciprocal appearance is stressed.

We are indebted to the physicians of the Hospital staff for their kind permission to use their cases in this report; the autopsies were performed by Dr. O. Saphir.

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MURAL THROMBI IN THE HEART

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IN 1809, Burns¹ differentiated endocardial thrombi from agonal and post-mortem clots and various tumor masses. Since then the morphology of mural thrombi has been well understood, but the mechanism of formation is still in doubt.

Hunter² (1794) thought that thrombi consisted of exudate from an infected vessel wall; Cruveilhier³ (1829) believed the reverse, namely, that the clot came first and the infection second. Andral⁴ (1842) postulated a combination of stasis and infection. Virchow⁵ (1855) first pointed out that sluggish circulation and changes in the quality of the blood might produce thrombosis without infection, and, in substantiation of this viewpoint, Zahn⁶ (1874) produced thrombosis by injuring vessel walls. Various other contributions have gradually led to the modern concept of the formation of thrombi, which stresses physical, chemical, and colloidal changes in the blood, as well as endothelial injury and stasis.

With regard to the etiology of mural thrombi, Harvey and Levine,⁷ after studying 111 mural thrombi which occurred in 2,091 consecutive autopsies, decided that myocardial degeneration and auricular fibrillation were most important. Cleland⁸ encountered sixty-nine mural thrombi in 3,000 autopsies, and stressed myocardial infarction and cardiac dilatation, with back pressure extending to the auricles. In 46.7 per cent of Meakins and Eakin's⁹ cases of coronary thrombosis there were mural thrombi. Blumer¹⁰ concluded that mural thrombi occurred in 50 per cent of cases of infarction. Graef, et al.,¹¹ found auricular thrombosis in 13 per cent of 178 rheumatic hearts. They concluded that mitral stenosis, congestive heart failure, auricular fibrillation, and localized inflammation favored the formation of auricular thrombosis in rheumatic heart disease.

The material for this study of mural thrombi consists of clinical and pathologic observations on 771 consecutive, adult, autopsied patients in whom heart disease was the chief cause of death. These cases occurred in 6,285 consecutive post-mortem examinations done at the Cleveland City Hospital from January, 1930, to June, 1939, inclusive.

Distribution of Mural Thrombi by Chambers.—Of the 771 patients, 265, or 34.4 per cent, had one or more ante-mortem, mural thrombi in the heart, as shown in Table I.

From Table I it is seen that in 170 cases (64.2 per cent) mural thrombi were found in only one chamber of the heart; the chambers involved,

Presented at the Sixteenth Annual Meeting of the American Heart Association, June 7, 1940, New York City.

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Received for publication June 24, 1940.

TABLE I
DISTRIBUTION OF MURAL THROMBI BY CHAMBERS

LOCATION	NO. OF CASES
Left ventricle alone	85
Right atrium alone	59
Right atrium and left ventricle	24
Right ventricle and left ventricle	24
Right atrium and left atrium	19
Left atrium alone	17
Right atrium, right ventricle, and left ventricle	11
Right ventricle alone	9
All four chambers	4
Right atrium and right ventricle	4
Right atrium, left atrium, and left ventricle	3
Right ventricle, left atrium, and left ventricle	3
Left atrium and left ventricle	2
Right atrium, right ventricle, and left atrium	1
Right ventricle and left atrium	0
Total	265

in decreasing order of frequency, were the left ventricle, the right atrium, the left atrium, and the right ventricle. In seventy-three cases (27.5 per cent) mural thrombi were present in two chambers. Three chambers were involved in eighteen cases (6.8 per cent), and all four chambers in four cases (1.5 per cent).

Further analysis shows that mural thrombi were found in the right and the left sides of the heart as given in Table II.

TABLE II

LOCATION	NO. OF CASES
Left side of the heart only	104
Right side of the heart only	72
Both sides of the heart	89
Total	265

Stated differently, one-third of 771 patients who died of heart disease had mural thrombi in one or more chambers of the heart; one-fourth had thrombi in the left side of the heart; one-fifth had thrombi in the right side of the heart; and one-ninth had mural thrombi in both sides of the heart.

The Incidence of Mural Thrombi in Various Types of Heart Disease.—The incidence of mural thrombi varied with the type of heart disease (Table III). Coronary artery disease, with coronary thrombosis and myocardial infarction, was the type of heart disease most likely to be associated with mural thrombi; two out of every three patients had this complication. Coronary artery disease without myocardial infarction and with or without hypertensive heart disease, hypertensive heart disease itself, and rheumatic heart disease were virtually alike, with mural thrombi in about one case in three. Only one of five patients who died of syphilitic heart disease had mural thrombi, and this complication was distinctly uncommon in cor pulmonale and subacute and acute bacterial endocarditis.

Coronary Artery Disease With Myocardial Infarction, With or Without Associated Hypertensive Heart Disease (133 Cases, in Eighty-nine of Which There Were Mural Thrombi).—Sixty per cent of the mural thrombi found in this group were located on the endocardial surface at the point of infarction. Evidence pointing to the etiological importance of infarction as a cause of mural thrombi is afforded by the fact that, of eighty-nine patients who had one myocardial infarct, fifty-five, or 61.8 per cent, had mural thrombi, whereas of thirty patients who had two or more infarcts, twenty-six, or 86.7 per cent, had mural thrombi; this is a significant difference.*

TABLE III
INCIDENCE OF MURAL THROMBI IN VARIOUS TYPES OF HEART DISEASE

TYPE OF HEART DISEASE	NO. OF CASES	NO. WITH MURAL THROMBI	PER CENT
Coronary artery disease with infarction (with or without hypertensive heart disease) ¹	133	89	66.9
Coronary artery disease without infarction (with or without hypertensive heart disease) ¹	94	33	35.1
Hypertensive heart disease	147	46	31.3
Rheumatic heart disease	116	37	31.9
Syphilitic heart disease	67	13	19.4
Cor pulmonale	50	3	6.0
Subacute bacterial endocarditis	30	1	3.3
Hypertensive heart disease complicated by various types of heart disease	15	7	46.6
Hypertensive heart disease complicated by rheumatic heart disease	13	6	46.2
Acute bacterial endocarditis	13	0	0.0
Coronary artery disease without infarction, complicated by various types of heart disease	10	4	40.0
Calcific stenosis	8	2	25.0
Thyroid heart disease	8	0	0.0
Obliterative pericarditis	7	0	0.0
Tuberculous pericarditis	7	0	0.0
Coronary artery disease with infarction, complicated by various types of heart disease	5	2	40.0
Undiagnosed	34	17	50.0
Miscellaneous	14	5	35.7
Total	771	265	34.4

¹Whether or not there was associated hypertensive heart disease made no appreciable difference.

The locations of the mural thrombi in this group are given in Table IV. The predominant frequency of thrombi in the left ventricle, the portion of the heart most often affected by infarction, is apparent.

There was no significant association between the occurrence of mural thrombi in this group and such factors as sex, age by decades, the number of attacks of congestive failure, the presence or absence of auricular fibrillation, and the degree of hypertrophy of the heart.

*In this article, the term "significant" refers to a difference which could be produced by chance in less than 5 per cent of trials, as demonstrated by application of the chi square test; "highly significant" refers to a difference so great that it could be produced by chance in less than 1 per cent of trials, again as demonstrated by application of the chi square test.

TABLE IV

LOCATION	NO. OF CASES
Left ventricle alone	46
Left ventricle and right ventricle	13
Left ventricle, right ventricle, and right atrium	8
Left ventricle and right atrium	7
Right atrium alone	6
Left ventricle, right ventricle, and left atrium	3
Right atrium and left atrium	2
Right ventricle alone	1
Right ventricle and right atrium	1
Left ventricle and left atrium	1
All four chambers	1
Total	89

Coronary Artery Disease Without Infarction, With or Without Associated Hypertensive Heart Disease (Ninety-four Cases, in Thirty-three of Which There Were Mural Thrombi).—The locations of the mural thrombi in this group are given in Table V.

TABLE V

LOCATION	NO. OF CASES
Left ventricle alone	13
Left ventricle and right atrium	6
Right atrium alone	4
Right atrium and left atrium	3
Right ventricle and left ventricle	3
Right atrium, right ventricle, and left ventricle	2
Left atrium alone	1
Right atrium, left atrium, and left ventricle	1
Total	33

No association could be demonstrated between the occurrence of thrombi and such features as sex, age, the number of attacks of congestive failure, the presence or absence of auricular fibrillation, and the degree of hypertrophy of the heart.

Uncomplicated Hypertensive Heart Disease (147 Cases, in Forty-six of Which There Were Mural Thrombi).—The distribution of the thrombi is given in Table VI.

TABLE VI

LOCATION	NO. OF CASES
Left ventricle alone	11
Right atrium alone	10
Right atrium and left ventricle	6
Right atrium and left atrium	5
Right ventricle and left ventricle	5
Right ventricle alone	3
Right atrium and right ventricle	2
All four chambers	2
Left atrium alone	1
Right atrium, left atrium, and left ventricle	1
Total	46

There was a significant association between the occurrence of mural thrombi and age, as shown in Table VII.

TABLE VII

DISTRIBUTION OF MURAL THROMBI ACCORDING TO AGE IN CASES OF HYPERTENSIVE HEART DISEASE

AGE GROUP	NO. OF CASES	PATIENTS WITH MURAL THROMBI	PER CENT
10-39	17	10	58.8
40-49	32	12	37.5
50-59	47	14	29.8
60-79	51	10	19.6

From Table VII it is seen that, whereas about 60 per cent of the patients below 40 years of age with hypertensive heart disease had mural thrombi, only 20 per cent of those who were 60 years of age, or older, showed this complication, a difference which is hard to explain.

There was no association between the occurrence of thrombi and such factors as sex, race, the number of attacks of congestive failure, the presence or absence of auricular fibrillation, or the degree of hypertrophy of the heart.

Rheumatic Heart Disease (116 Cases, in Thirty-seven of Which There Were Mural Thrombi).—Auricular fibrillation bore a highly significant relation to the occurrence of mural thrombi in patients with rheumatic heart disease, for among sixty patients with auricular fibrillation there were twenty-six with mural thrombi (43.3 per cent) whereas, among fifty patients with normal cardiac mechanism, there were only nine with mural thrombi (18 per cent). In no other type of heart disease could a significant association between auricular fibrillation and the occurrence of mural thrombi be demonstrated. This paradox is probably best explained by the fact that auricular fibrillation is likely to be present over a longer period of time in cases of rheumatic heart disease than in any other type of heart disease.

The distribution of thrombi by chambers is given in Table VIII.

TABLE VIII

LOCATION	NO. OF CASES
Left atrium alone	13
Right atrium alone	12
Right and left atria	7
Right ventricle alone	3
Left ventricle alone	1
Right and left ventricles	1
Total	37

The predominant frequency of thrombi in the atria (86.5 per cent) is probably to be explained by the fact that over 50 per cent of these patients had auricular fibrillation, with consequent stagnation of blood in the atria; the importance of this has been indicated.

There was a highly significant association between age and the occurrence of mural thrombi in this group, as shown in Table IX.

From Table IX it is apparent that mural thrombi occurred more often in the older patients. This fact is also probably related to the pres-

TABLE IX

DISTRIBUTION OF MURAL THROMBI ACCORDING TO AGE IN CASES OF RHEUMATIC HEART DISEASE

AGE GROUP	NO. OF CASES	PATIENTS WITH MURAL THROMBI	PER CENT
10-39	55	10	18
40-49	23	9	39
50-79	38	18	47.4

ence or absence of auricular fibrillation, for 68.4 per cent of these older patients had auricular fibrillation, whereas fibrillation occurred in only 39.6 per cent of the younger patients; this difference is highly significant. This increasing incidence of mural thrombi in the older patients with rheumatic heart disease is exactly the opposite of the situation in hypertensive heart disease.

Although thrombi occurred 10 per cent more often in cases in which there had been two or more attacks of congestive failure than in those in which there had been only one, this difference was not significant statistically. No association between mural thrombi and sex or degree of hypertrophy of the heart was demonstrable.

Syphilitic Heart Disease (Sixty-seven Cases, in Thirteen of Which There Were Mural Thrombi).—The distribution of the thrombi is given in Table X.

TABLE X

LOCATION	NO. OF CASES
Right atrium alone	9
Right ventricle alone	1
Left atrium alone	1
Left ventricle alone	1
Right atrium and right ventricle	1
Total	13

There was no association between the occurrence of thrombi and sex, age, number of attacks of congestive failure, cardiac mechanism, or degree of cardiac hypertrophy.

SUMMARY

Of 771 consecutive, adult, autopsied patients who died of heart disease, 265, or 34.4 per cent, had one or more mural thrombi. Coronary artery disease, with myocardial infarction, was the type of heart disease most often associated with mural thrombi; in two-thirds of these cases this complication was present. Mural thrombi were associated with coronary artery disease without myocardial infarction, hypertensive heart disease, and rheumatic heart disease, in one-third of the cases; they were present in one-fifth of the cases of syphilitic heart disease, but were uncommonly found in cases of cor pulmonale and bacterial endocarditis.

Most of the mural thrombi in cases of coronary artery disease with myocardial infarction were caused by the infarction itself and were located in the left ventricle.

In hypertensive heart disease, about 60 per cent of the patients below 40 years of age had mural thrombi, whereas only 20 per cent of those who were 60 years of age or older had this complication. This significant difference is unexplained.

In rheumatic heart disease, mural thrombi occurred two and a half times as often in patients with auricular fibrillation as in those with normal mechanism; this is highly significant. The thrombi were present in the right atrium and/or the left atrium in 86.5 per cent of the cases, and this is probably another indication of the importance of auricular fibrillation. There was a highly significant preponderance of mural thrombi in older patients, presumably because of the greater frequency of auricular fibrillation in this group.

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DISCUSSION

DR. S. A. LEVINE, Boston.—One unanswered question that is of great importance to us practically is, when do the thrombi form? We know pretty clearly when they form in the left ventricle after coronary occlusion. I think there is sufficient evidence that thrombosis of the left ventricle follows, rather than precedes, the infarction. Thrombi in the auricles were the immediate cause of death in 20 per cent of all cases of rheumatic heart disease at the Brigham Hospital. It is a big problem, but we do not know when the thrombus forms. Even the role that fibrillation plays is not altogether clear. We found a very high incidence of mural thrombosis in the auricles in cases of mitral stenosis with normal rhythm, and I suggest that Dr. Garvin would find that the average age at death of the patients with normal rhythm was a good deal less than that of the patients with auricular fibrillation. Therefore, those with fibrillation had a few years longer to produce mural thrombosis. We must admit that fibrillation, per se, must be play-

ing a role because of the rare experience, and it is a rare one, but one that we should bear in mind, namely, that a thrombus can form in the auricles in cases of so-called normal persons with fibrillation.

I had the experience of seeing such a patient; he had no hypertension or coronary disease, but had fibrillation without symptoms except palpitation. Later he developed a left mural thrombus.

I think we still need to reconsider the exact role that auricular fibrillation plays in cases of mitral stenosis and what part the time element plays. The longer a person with heart disease lives, the more opportunity there is to have a mural thrombus.

It is interesting that thrombi were very rare in cases of subacute bacterial endocarditis. One would have expected, as a matter of chance, that more thrombi would have been found; this makes one think that these patients who have subacute bacterial endocarditis are running an entirely different clinical course, and that their reactions differ from those of patients with other kinds of rheumatic hearts. They have less reactivation of the rheumatic infection. If we knew when the thrombus is due to form or might be formed, we would be challenged to stop it or dissolve it. Nowadays, with the introduction of heparin, we must be thinking about the possibility of preventing mural thrombosis in heart disease because it is not only found at autopsy, but is an important cause of death in an appreciable number of patients.

It is interesting that thrombi occurred in so-called hypertensive heart disease. That term is commonly used in diagnosis, but I do not think it explains the disease. I see no reason why, in real hypertensive heart disease, there should be thrombosis, and the occurrence of this thrombosis in hypertensive heart disease in the young, that is, from 10 to 39, means to me that something other than hypertensive heart disease was the cause of death, and that the diagnosis of hypertensive heart disease was not correct.

DR. ROBERT L. LEVY, New York.—I should like to ask two questions. First, was the incidence of mural thrombi related in any way to the presence or absence of congestive failure? Second, was there any relationship, in the various groups, between the presence of mural thrombi and the occurrence of embolism?

DR. CURTIS F. GARVIN, Cleveland.—In regard to Dr. Levy's question, virtually all of these patients had heart failure; they died of heart disease. The only exceptions of any consequence would be in some of the cases of coronary thrombosis and subacute bacterial endocarditis. Second, I did not investigate embolism. I presume the fact that there was heart failure accounted for the occurrence of mural thrombi in hypertensive heart disease.

THERAPEUTIC VENOUS OCCLUSION

ITS EFFECT ON THE ARTERIAL INFLOW TO AN EXTREMITY, AS MEASURED
BY MEANS OF THE REIN THERMOSTROMUHR*

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THERAPEUTIC venous occlusion is a subject which has been under discussion for the last thirty years. The question of what effect it has upon the arterial inflow to an extremity has never been satisfactorily answered. In acute arterial insufficiency, the evidence from a clinical point of view indicates that there is an increase in the arterial blood flow following venous occlusion. In chronic obliterative vascular disease, more evidence is accumulating to show that the blood flow may be increased by the same method.

The following brief review of the literature is of interest in a reconsideration of this problem. Oppel,¹ in 1913, reported beneficial results following ligation of the femoral vein in six cases of arteriosclerotic obliterative disease. Lilienthal,² in 1914, and Ginsburg,³ in 1917, advocated femoral vein ligation in thromboangiitis obliterans. Morton and Pearse,⁴ in 1928, and Van Gorder,⁵ in 1929, noted favorable results from therapeutic venous occlusion in obliterative vascular disease. Although there was considerable evidence that the circulation could be improved by high venous ligation, the results fell short of what had been anticipated, so that the operation has fallen into disrepute. Collens and Wilensky,^{6, 21} in 1936, introduced a nonoperative method of producing intermittent venous occlusion; it was obtained by applying a pneumatic tourniquet to the proximal portion of an extremity. The tourniquet is connected to an electrically controlled pump, which inflates it at regular intervals and automatically releases the pressure. This type of venous occlusion has proved to be of value, in both acute and chronic obliterative vascular disease, in the development of a collateral circulation to an extremity with deficient arterial supply.

Following acute occlusion of a major artery to an extremity, there is practically universal agreement that ligation of the concomitant vein is beneficial. Makins,⁷ reporting on his experiences in the British Army Medical Service during the world war of 1914-1918, stressed the importance of ligating the concomitant vein when it is necessary to ligate a major artery to a limb. He is reported to have recognized this first during the Boer war, 1899-1901, and it was largely through his studies

From the Surgical Laboratories of the Harvard Medical School at the Massachusetts General Hospital.

*Acknowledgment is made for the invaluable aid given in the construction of the thermostromuhr by Walter S. Rogers, radio engineer of the Research Division of the United Shoe Machinery Corporation, Beverly, Mass., and to Adelbert L. Libby, Surgical Laboratories of the Harvard Medical School at the Massachusetts General Hospital, for his skill and patience in constructing the blood flow units.

Received for publication June 24, 1940.

that the Interallied Congress of Surgeons, in 1917, accepted the principle of simultaneous ligation of the vein. He reported 172 cases of injury to the arteries of the extremity, in which the artery alone was ligated in 101, with gangrene in twenty-nine cases, or 28 per cent, and seventy-one cases in which both artery and vein were ligated, with gangrene in fourteen, or 19.7 per cent. Tuffier,⁸ in 1917, reported that ligation of the popliteal artery alone in twenty-four cases gave favorable results in fourteen, or 58.33 per cent, and led to gangrene in ten, or 41.66 per cent, whereas simultaneous ligation of the artery and vein in twenty-eight cases produced favorable results in twenty-two, or 78.6 per cent, and caused gangrene in only six, or 21.4 per cent. Sehrt,⁹ in 1916, reported similar results when the artery alone was ligated; gangrene occurred in 20.4 per cent of the cases, whereas it was seen in only 9 per cent when both the artery and vein were tied. Heidrick,¹⁰ in 1921, reported an incidence of gangrene of 15.4 per cent in 995 cases after ligation of a large artery, whereas the incidence was only 8.5 per cent in 198 cases in which both the artery and vein were ligated. Holman,¹¹ in 1927, and Pemberton and McCaughan,¹² in 1932, recommended simultaneous vein ligation.

Experimental investigations of this improvement in the circulation after venous occlusion have not given uniform results. Brooks and Martin,¹³ in 1923, confirmed the clinical results by experiments carried out on a series of rabbits. They found that, when the common iliac or external iliac arteries were ligated, gangrene developed in 71.5 per cent of the animals, whereas, in a second series, in which there was added to this procedure ligation of the common iliac vein, the incidence of gangrene was only 33.3 per cent. These results were corroborated by Holman,¹¹ in 1927. He found that, when the common iliac artery and inferior vena cava were ligated simultaneously in eighteen rabbits, only two developed gangrene. In ten other rabbits in which the common iliac and external iliac arteries and the inferior vena cava were simultaneously ligated, there were no cases of gangrene, so that, of twenty-eight animals, gangrene developed in only 7.1 per cent.

Attempts have been made to explain the improvement of the circulation which results from simultaneous vein ligation in both clinical and experimental acute arterial occlusion. Studies have been carried out by several investigators to ascertain the effect of venous occlusion on the arterial flow of the extremity. Brooks and Martin,¹³ in 1923, studied the effects of simultaneous ligation of the vein and artery of a dog's leg, under anesthesia, by measuring the temperature of the tissues distal to the ligature. In these experiments they found a decrease distal to the ligature after ligation of the concomitant vein and acute arterial occlusion, and from this they assumed that the volume flow had decreased. The most recent experimental work with reference to this subject was reported by Montgomery,¹⁴ in 1932. It supports Brooks and Martin's studies on tissue temperature. He used a direct, continu-

ous volume flow apparatus, which was a modification of the Ludwig stromuhr and Stolinkow's double inlet-outlet apparatus, to measure the arterial inflow before and after venous ligation. He concluded that ligation of the concomitant vein after ligation of the superficial femoral artery resulted in no change, or a slight decrease, in the volume flow in the iliac artery, and a more marked decrease when the venous return was obstructed proximal to the site of arterial occlusion. Halsted¹⁵ expressed the opinion purely from theoretical grounds that obstruction of the venous return may disturb the development of a collateral circulation following acute arterial occlusion, whereas La Roque¹⁶ felt that therapeutic vein ligation favored the development of collateral vessels.

Holman,¹¹ in 1927, and Theis,¹⁷ in 1928, reported an increase in the volume flow of blood after concomitant venous obstruction. Their method of determining the blood flow was to cannulate the artery distal to the point of arterial obstruction and measure the amount of blood which flowed from the cannula over a given period of time, before and after venous ligation. Both of these investigators found that the amount of blood flowing from the cannula was increased after venous obstruction. This method, however, was open to considerable criticism, as it was argued that it merely measured the collateral arterial blood flow, which could more readily pass out through the open artery than it could by way of the venous collateral channels after the main vein had been obstructed. Pearse,¹⁸ in 1927, and Spurrell,¹⁹ in 1930, studied the arterial tree in experimental animals after ligation of the main artery to an extremity, both with and without simultaneous venous ligation. They found that, in the former, the collateral arterial blood supply was developed to a much greater extent than in the latter.

Lewis and Grant,²⁰ who studied the reactive hyperemia which results from venous congestion in unanesthetized human subjects, made a very important observation. Their method of measuring blood flow to the extremity was by means of venous obstruction, using a plethysmograph to measure the change in size of the extremity. They noted that their plethysmographic tracings showed, during the period of venous congestion, a marked increase in the amplitude of the arterial pulsations. They state: "At the end of ten or fifteen minutes, the increased amplitude (of the arterial pulsations) is usually maximal and is then unmistakable. This increase in the size of the volume pulse forms a first suggestion that *venous engorgement causes dilatation of the vessels on the arterial side.*"* Collens and Wilensky,²¹ in 1936, noted this observation of Lewis and Grant, but nevertheless considered that the increase in arterial inflow *following* the release of venous occlusion was of more significance. From this review of the literature it is clear that there is still a controversy as to whether therapeutic venous occlusion does or does not increase the arterial inflow to an extremity.

*Authors' (Lewis and Grant) italics.

The purpose of this paper is to present further evidence which was obtained in a series of experiments on dogs. A thermostromuhr method which has been perfected in the Surgical Laboratories of the Harvard Medical School at the Massachusetts General Hospital was used for measuring blood flow. By means of this method, it is possible to measure accurately the minute volume flow of blood in an artery or vein without disturbing the continuity of the blood vessel; this gives it an advantage over other methods. The principle of the thermostromuhr is similar to that of the one originally described by Rein,²² and later by Herriek and Baldes.²³

EXPERIMENTAL STUDIES

The following is a short description of the thermostromuhr method of measuring the blood flow. The blood is heated at a given point by means of a radio frequency current which is passed through the blood vessel between two platinum electrodes on opposite sides of the vessel. The electrodes are placed equidistant between two thermojunctions, made of copper and constantan wire, that are connected with a galvanometer (Fig. 1). These are joined in series and are known as a differential thermocouple. The platinum electrodes and the thermojunctions are imbedded in a specially constructed bakelite block, as it is important that the radio frequency heating current be completely insulated from the thermocouple circuit. Rubber-covered, insulated wires, to be referred to as leads,* carry the heating current to the electrodes, and similar ones carry the direct current from the thermocouple to a galvanometer. With a given amount of heating current, the galvanometer deflection varies inversely with the volume flow of blood.

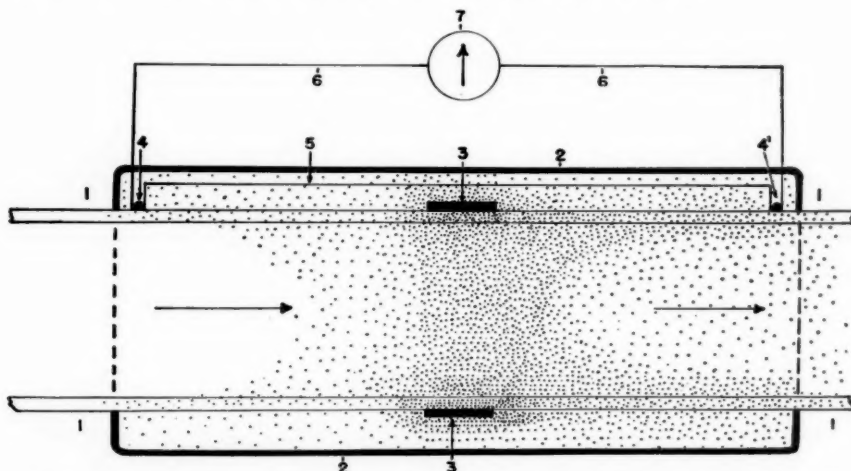


Fig. 1.—A schematic diagram of the application of a blood flow unit to a blood vessel. 1, Blood vessel wall; 2, blood flow unit; 3, platinum electrodes; 4, 4', thermojunctions; 5, constantan wire; 6, copper leads; 7, galvanometer.

The bakelite block in which these wires and electrodes are imbedded contains a groove into which the blood vessel fits (Fig. 2). It is necessary that one have a very tight fit, so that the vessel wall is in apposition with the electrodes and the side of the bakelite block where the thermocouples are imbedded. For this reason

*Acknowledgment is made to the Simplex Wire & Cable Co., Cambridge, Mass., for their cooperation and aid in the construction of these leads, which are specially constructed, rubber-insulated, multiple-strand, copper-tinsel wires.

it is necessary to have a fairly large number of these units, in order to be sure of obtaining a proper fit; otherwise, erroneous readings are obtained. The proper construction of these units is one of the prime requisites for the successful operation of this method of measuring blood flow. The blood flow studies were carried out on dogs which weighed between 15 and 25 kg. They were anesthetized by the intravenous injection of a 10 per cent solution of sodium amytal. The initial dosage was 50 to 60 mg. per kg. of body weight. It was given in one of the forepaw veins, in order to keep the venous system of the hind leg intact for experimental studies. At varying times during the experiment it was necessary to give additional sodium amytal in 50- to 100-milligram doses intravenously. In the first few experiments the studies were made on the right femoral artery and vein, but in the later

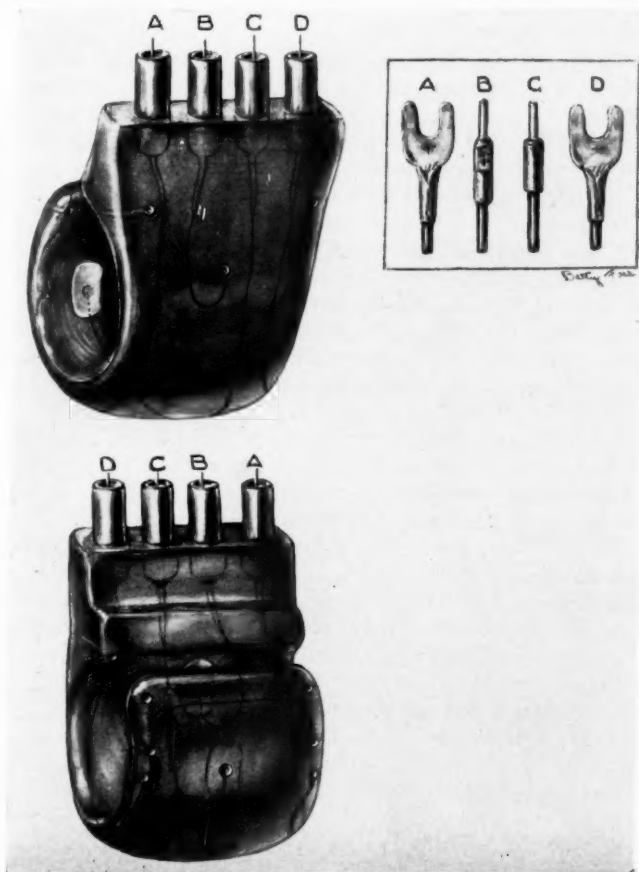


Fig. 2.—A complete blood flow unit, showing the front and back views. A and D, Galvanometer leads; B and C, radio frequency leads. The inset shows the terminals on the leads. (These units are made in the Surgical Laboratories of the Harvard Medical School at the Massachusetts General Hospital.)

experiments the iliac artery and vein, usually on the right side, were used. The latter vessels were exposed by an extraperitoneal approach, as it was found that the animals withstood the experiments much better if the abdominal cavity was not opened. In some cases the inferior vena cava and the common iliac, external iliac, and femoral veins were also dissected out, in order to test the effect on the arterial flow of occlusion of these different veins. Arterial blood pressure was

measured by cannulating one of the carotid arteries. The venous pressure in the extremity which was being studied was measured by cannulating a vein in the lower part of the leg, usually one of the superficial ones. Clotting in this system was prevented by connecting the cannula with a reservoir of saline which contained heparin. In this way it was found unnecessary to heparinize the animal completely. In order to place one of the blood flow units on a vessel, it is necessary to dissect it completely free from the tissues about it for a distance of about 2 cm. Great care was taken not to traumatize the artery while dissecting it free, for even the slightest trauma would throw it into marked vasoconstriction. At the same time, it was extremely important that the wall of the vessel be cleaned thoroughly of excess tissue. Occlusion of the veins was produced by passing silk ligatures around them. Both ends of the ligature were then passed out through a glass tube of small caliber. The tube was inserted through a small stab wound in the skin, and pushed directly through the muscles and fascia, so that the inner end of it was in close approximation to the vein. The glass tube was then fixed by means of clamps to prevent it from moving when traction was exerted on the silk thread. In this manner it was possible to impinge the vein against the inner end of the tubing, and thus produce complete occlusion of the vessel. Releasing the ligature, in most instances, if the glass tubing had been correctly placed, would relieve the venous obstruction.

After careful dissection of the femoral or iliac artery, the vessel was measured and the correct unit applied to it. The unit was fixed in place by suturing it to the adjacent muscles; this was done in order to prevent displacement in case there was undue traction on the leads. After it was ascertained that the venous ligatures and the unit were properly placed, the wound was closed in layers. In one animal the blood flow unit was placed on the iliac artery, under aseptic precautions. The effect on the arterial blood flow of venous congestion produced by a pneumatic tourniquet on the thigh and digital compression of the femoral artery were studied without anesthesia. These experiments were carried out the day after the operation (Fig. 9). Experiments were done on ten other dogs, under sodium amytal anesthesia. After the completion of an experiment, the animal was sacrificed by bleeding it from the carotid artery. The blood was collected and defibrinated.

The vessel and the blood flow unit were removed intact. They were placed in a constant temperature calibrating apparatus (Fig. 3), surrounded by blood from the same animal. The blood vessel was connected with a circulating system containing the defibrinated blood. By means of this apparatus, it was possible to maintain the blood pressure which the animal had had during the experiment, and also to vary the volume flow per minute through the vessels. The galvanometer deflection was recorded for each rate of blood flow. In this way a calibration curve was obtained, and, by means of it, it was possible to ascertain the actual amount of blood flow through the iliac artery in the dog by referring to the records taken at the time of the experiment. The different experiments carried out on this group of animals have been divided into six series.

RESULTS

Series 1. The Effect of Venous Occlusion in the Ipsilateral Limb on the Normal Arterial Blood Flow to an Extremity.—The blood flow through a dog's femoral artery was measured before, during, and after occlusion of the ipsilateral femoral vein for periods varying from two to thirty-four minutes. The femoral artery and vein on the right side were dissected free through a small skin incision. A blood flow unit of the proper size was placed on the femoral artery, and a silk ligature was

placed around the femoral vein, as previously described. A record of the blood flow, as measured by the galvanometer deflection, was made on photographic paper. The blood flow before the occlusion was usually found to be very constant, providing the animal was not too lightly anesthetized. In some cases, if the dog was shivering even though anesthetized, there were marked fluctuations in the blood flow. A supplementary injection of sodium amytal would stop the shivering, and then the blood flow would immediately become stabilized. As a record of the normal flow was being taken, sufficient traction was exerted on the suture around the femoral vein to occlude it completely. Within a very few seconds there was a very rapid and marked increase in arterial blood flow (Fig. 4). This was constant, regardless of whether the measurements were on the femoral or iliac artery. The flow usually reached a maximum within one minute, where it remained a short time. It then

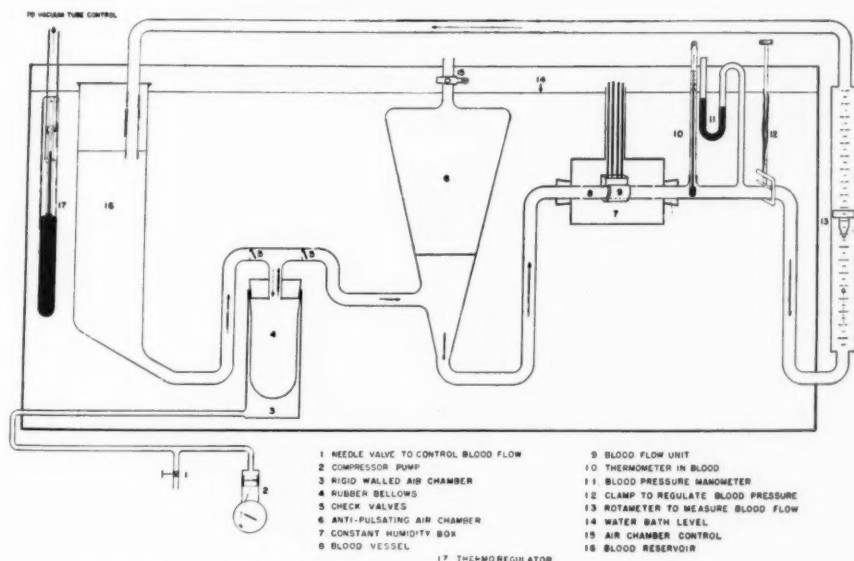


Fig. 3.—A schematic diagram of the constant temperature calibrating apparatus.

decreased gradually to a constant level that was always 30 to 50 per cent above normal. In one case, occlusion of the femoral vein was carried out for a period of thirty-four minutes (Fig. 4). In most cases, on release of the venous occlusion there was a very rapid and sudden decrease in the arterial blood flow, well below the normal level. This effect was only transitory, lasting ten to thirty seconds. Then the flow returned to a level between the maximum and the normal (Fig. 4). In the animal in which the occlusion lasted thirty-four minutes, the blood flow had returned to the normal level within one to two minutes after the release of the femoral vein, and in five minutes it was found to be less than before the occlusion was produced. In the record shown

(Fig. 4), the flow during three-minute occlusion increased from approximately 100 c.c. per minute to 230 c.c. a minute within the first minute of occlusion; after this there was a gradual decline in the volume flow to about 140 c.c. a minute at the end of the three-minute period. In the experiment in which the occlusion lasted thirty-four minutes, the initial flow was around 110 c.c. a minute; after the occlusion this increased to approximately 155 c.c. a minute, then fell to about 145 c.c. a minute, where it became stabilized and remained until the termination of the venous occlusion, as the tracing and graph show (Fig. 4).

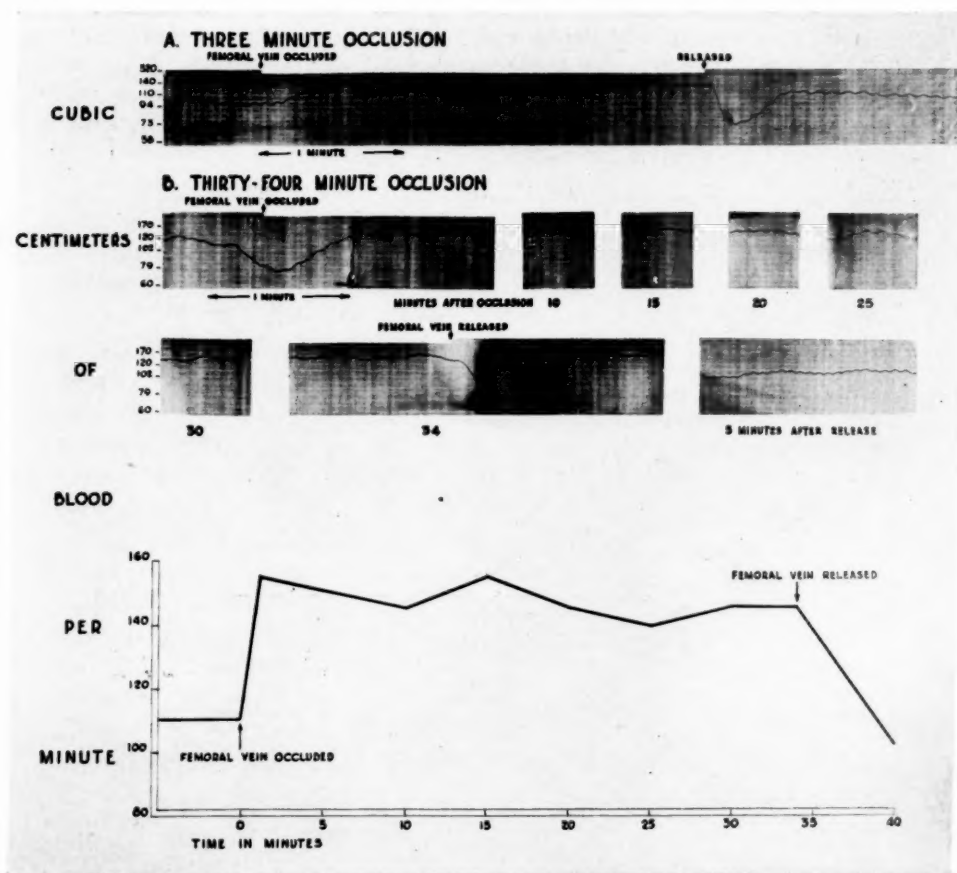


Fig. 4.—The effect of venous occlusion in the ipsilateral limb on the normal arterial blood flow to an extremity (sodium amytal anesthesia). Note the rapid increase in the femoral artery blood flow after occlusion of the femoral vein in the three-minute occlusion record, namely from 100 c.c. per minute to 230 c.c. per minute. In the thirty-four-minute record, the increase is from 110 c.c. per minute to 155 c.c. per minute. It is also to be noted that the blood flow persisted at 145 c.c. per minute until the femoral vein was released. This shows that the increase in arterial blood flow is concomitant with the venous occlusion.

From this series of experiments it was clear that obstruction of the ipsilateral femoral vein in the presence of a normal femoral arterial blood flow increased the blood flow through the femoral artery for

a short period by more than 100 per cent, and that, over a prolonged period of time (one-half hour), a 33 per cent increase persisted.

Series 2. The Effect of Venous Occlusion in the Contralateral Limb on the Normal Arterial Blood Flow to an Extremity.—It was thought important to investigate whether this increase in arterial inflow was a local effect in the extremity in which the occlusion was produced, or whether it was a generalized effect, caused perhaps by a humoral or a nervous mechanism. Therefore, the blood flow through a dog's femoral artery was measured before, during, and after occlusion of the contralateral femoral vein for two- and three-minute periods. The results of these experiments are shown in Fig. 5. In one case the arterial blood flow was approximately 60 c.c. before, during, and after venous occlusion. In the other it remained around 110 c.c. per minute. Comparison of the latter record with those in Fig. 4 shows very well the different effect on the arterial inflow which is produced by occlusion of the ipsi- and the contralateral femoral veins in the same animal. It seemed from these experiments that the increased arterial inflow produced by venous occlusion was localized to the extremity in which the venous occlusion was produced, and that it was not a generalized effect.

Series 3. The Effect of Venous Occlusion on the Iliac Artery Blood Flow in the Presence of Acute Arterial Insufficiency.—In this group of experiments the effect of occlusion of the ipsilateral common iliac vein on the blood flow through the iliac artery was measured after occlusion of the femoral artery. The blood flow unit was placed on the iliac artery in the usual manner, and a suture was passed around the common iliac vein proximal to the level of the unit. A similar suture was placed on the femoral artery below the inguinal ligament. The locations of these various sites are shown in Fig. 6. Examination of the blood flow records from one of these experiments (Fig. 7) shows that there was a marked diminution in the arterial inflow through the iliac artery after occlusion of the femoral artery; it declined from approximately 450 c.c. a minute to about 60 c.c. a minute. Then, after occlusion of the iliac vein, there was a marked increase in the blood flow, reaching about 140 to 150 c.c. a minute. It should be noted that the increase in the arterial flow after venous occlusion in this experiment occurred much less rapidly than when the entire arterial blood supply was intact. In the latter instance, the arterial inflow reached a maximum within one-half to one minute, whereas, in this experiment, the blood flow after venous occlusion required two and one-half minutes to reach a maximum. It seems reasonable that such should be the case, for there is less blood entering the limb, and, as a result, the venous reservoirs of the leg are filled much more slowly than when the blood supply is intact. The significance of these observations will be discussed later. After release of the iliac vein, the arterial blood flow returned to the level where it had been previous to its occlusion. Release of the femoral

artery resulted in a blood flow which was slightly greater for a few minutes than the preocclusion figure (evidence of a slight reactive hyperemia); it then returned to the previous level. The blood pressure throughout this experiment (Fig. 7) showed essentially no change.

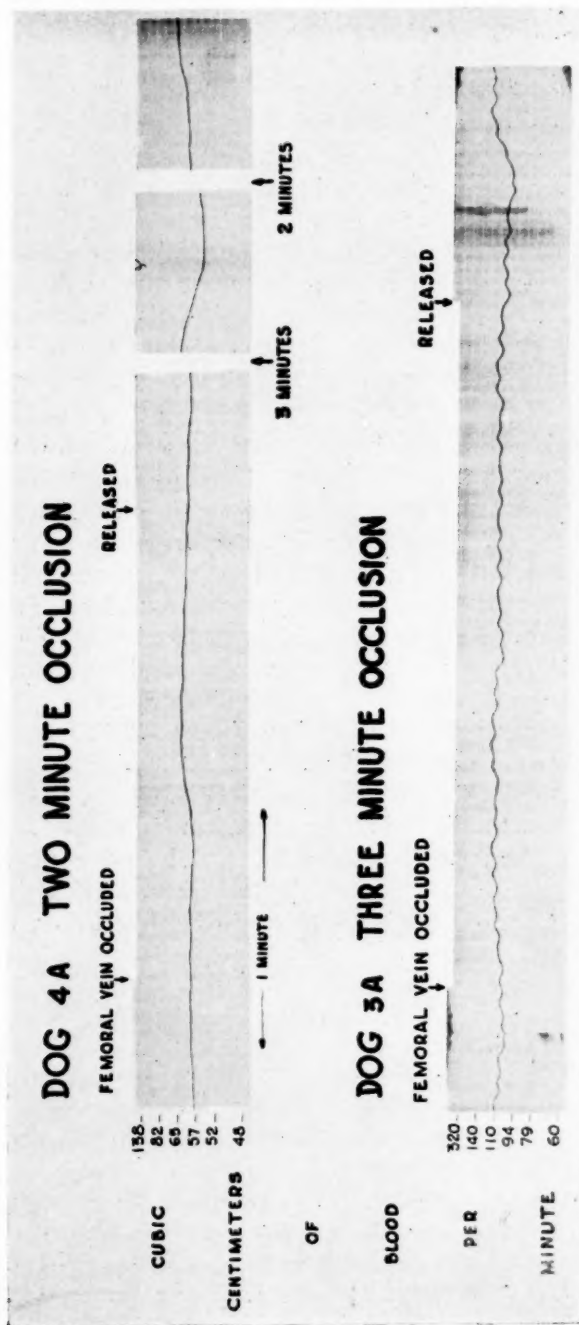


Fig. 5.—The effect of venous occlusion in the contralateral limb on the normal arterial blood flow to an extremity (sodium amytal anesthesia). Note that there is practically no change in blood flow after the venous occlusion, nor upon its release, in either of these records. Compare the three-minute occlusion in dog 3A in this figure with the three-minute occlusion in Fig. 4, as these records were taken on the same animal. Note the marked difference in the effect on the arterial blood flow.

Series 4. The Comparative Effect on the Iliac Artery Blood Flow Produced by Occlusion of the Femoral and External and Common Iliac Veins.—The animals in this experiment were prepared like the others, except that, in addition to placing the blood flow unit on the iliac artery, silk threads were placed around the common iliac vein, the external iliac vein, and the femoral vein, so that each one of these vessels could be occluded separately. The venous pressure in the lower part of the leg was also recorded. The effect of occlusion of the femoral, then the external, and finally the common, iliac vein is shown in Fig. 8A. It is to be noted that the iliac artery blood flow increased from approximately 115 c.c. per minute to about 145 c.c. per minute;

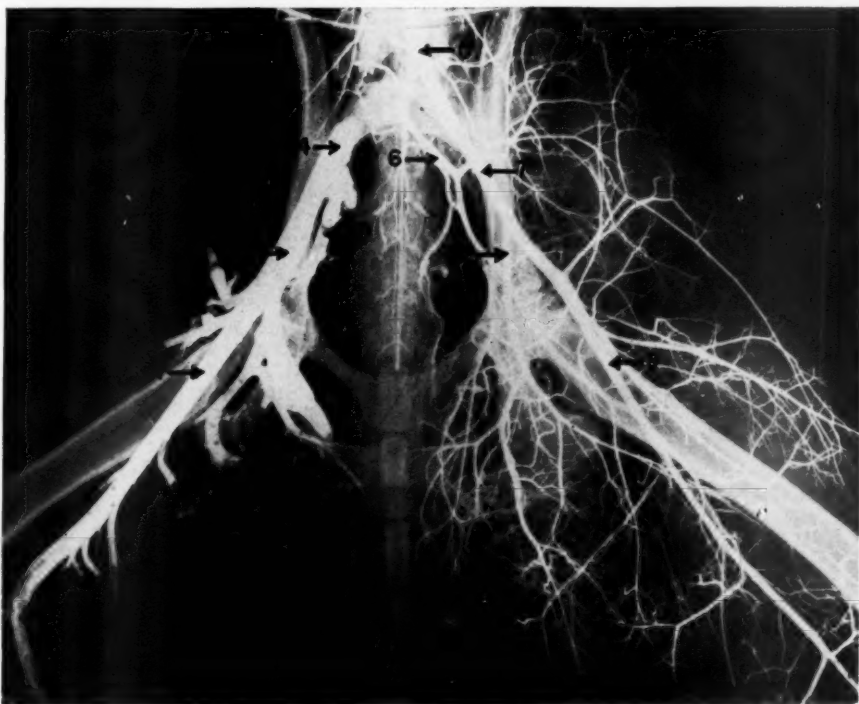


Fig. 6.—The arterial and venous system of a dog's hind leg, injected with barium sulfate. 1, Femoral vein, 2, external iliac vein; 3, internal iliac vein; 4, common iliac vein; 5, aorta; 6, hypogastric artery; 7, iliac artery; 8, deep femoral artery; 9, femoral artery (below the inguinal ligament).

coincidentally, there was a rise in the venous pressure from 5 to 22 mm. of mercury. The external iliac vein was then occluded after one and one-half minutes, without releasing the femoral vein. There was a further increase in the blood flow to approximately 210 to 215 c.c. a minute, and also an elevation in the venous pressure to 25 mm. With both of these veins shut off, the common iliac vein was finally occluded for a minute and a half. This produced very little, if any, change in the blood flow through the iliac artery or in the venous pressure level. The failure of the latter to increase is thought to explain

the lack of an increase in blood flow following occlusion of the common iliac vein. From this experiment it appears that the increase in arterial inflow which is produced by venous occlusion bears a direct relationship to the level of the venous pressure. This fact is further borne out in the following experiment.

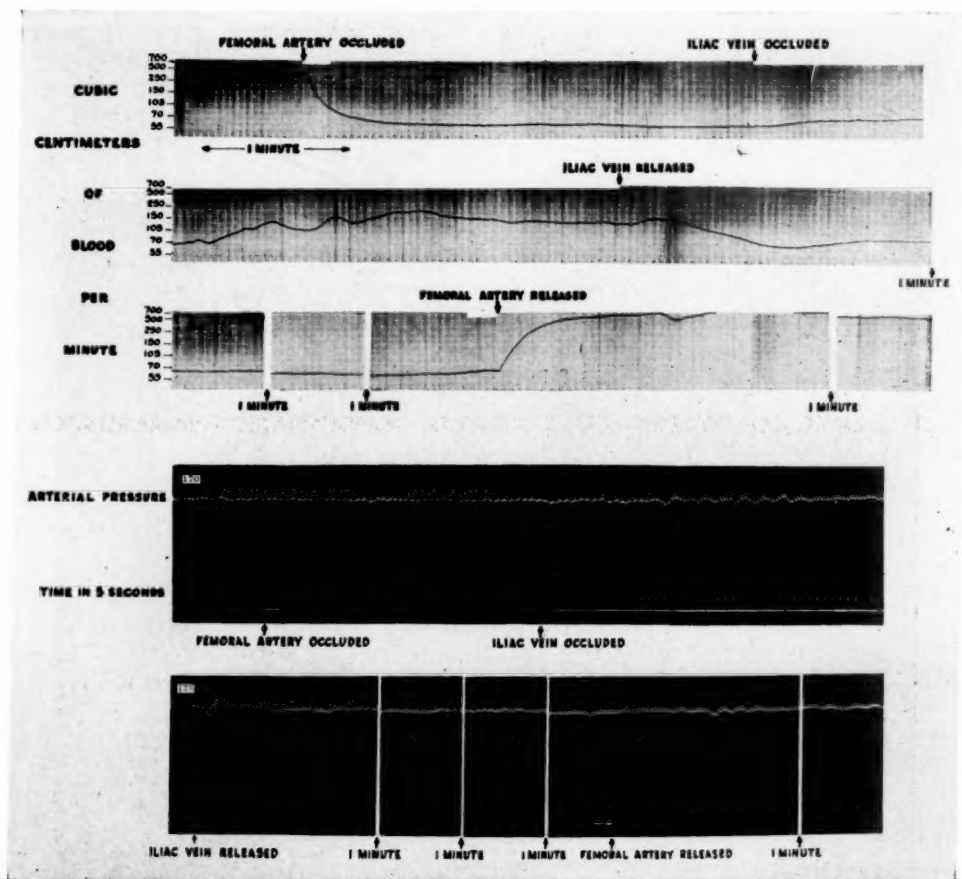


Fig. 7.—The effect of venous occlusion on the iliac artery blood flow in the presence of acute arterial insufficiency (sodium amytal anesthesia). After occlusion of the femoral artery, note the decrease in arterial blood flow from 450 c.c. a minute to 60 c.c. a minute, and the increase in blood flow to 140 or 150 c.c. a minute after occlusion of the iliac vein. It will be seen that this increase persisted as long as the occlusion was present, and that, after the release of the iliac vein, the flow returned to the preocclusion level. This experiment had no effect on the blood pressure of the animal.

Series 5. The Effect on the Iliac Artery Blood Flow of Increasing Venous Pressure by Applying a Pneumatic Tourniquet to the Thigh.—These experiments were carried out on the same animals which were used in Series 4. It was therefore possible to compare the relative effects of occluding the main veins of the extremity with those produced by a tourniquet placed around the upper part of the thigh. It seems probable there should be a difference, for occlusion of the vessels

themselves leaves collateral venous channels open, through which blood may return to the heart, whereas occlusion by means of a tourniquet must affect all of the venous channels. In the latter instance, blood gets back to the heart only when the pressure in the venous channels becomes sufficiently high to equalize and overcome that of the tourniquet.

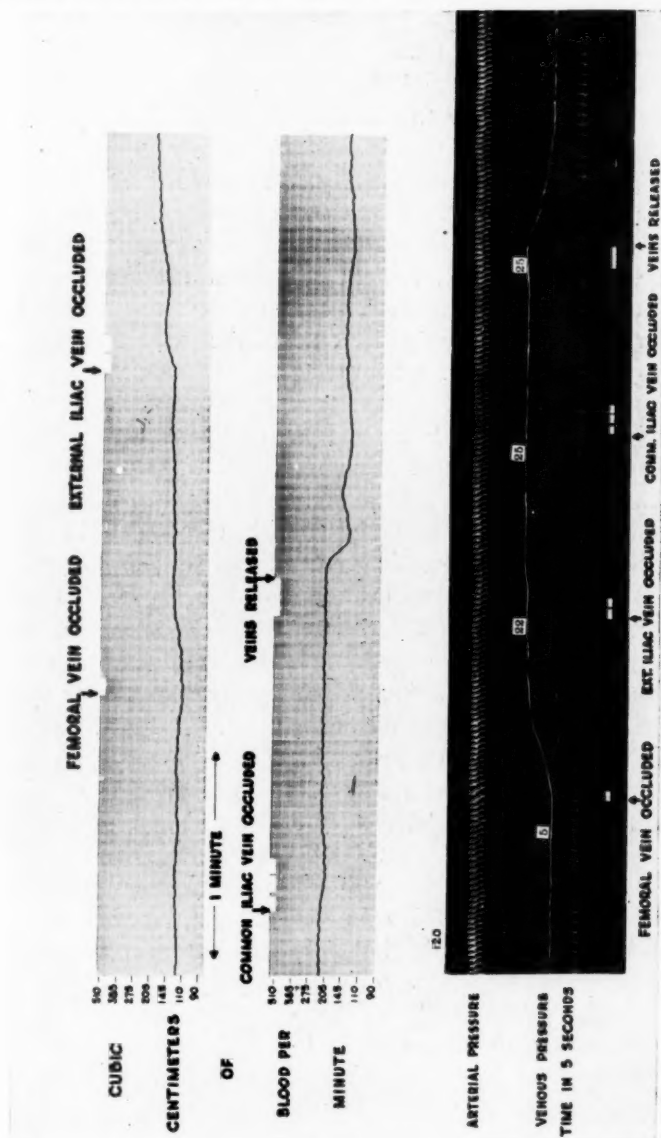


Fig. 8A.—The comparative effect on the iliac artery blood flow produced by occlusion of the femoral, external iliac and common iliac veins (sodium amytal anesthesia). The effect of occlusion of these veins is to be noted, both in reference to arterial blood flow and also the venous pressure in the limb. There was no increase in the arterial inflow after occlusion of the common iliac vein, nor was there any increase in the venous pressure. Compare these records with those in Fig. 8B.

In this series of experiments, the blood flow unit was placed in the usual manner on the iliac artery, the carotid artery was cannulated for the measurement of the arterial blood pressure, and one of the superficial veins of the lower leg was cannulated for measuring venous pressure. The blood flow at the normal venous pressure, before apply-

ing the tourniquet, was measured; then the tourniquet was inflated to a pressure of 40 mm. of mercury. This produced a rise in the venous pressure of the leg to 18 mm. of mercury within a minute. The blood flow in the iliac artery increased from a basal level of between 115 and 120 c.c. a minute to 150 c.c. a minute. When the tourniquet pressure was increased to 60 mm. of mercury the venous pressure rose to 40 and the blood flow increased to 205 c.c. a minute. The tourniquet pressure was then raised to 80, which brought the venous pressure up to 60 mm. of mercury and the blood flow to 250 c.c. a minute. The tourniquet pressure was further increased to 100 mm. of mercury, whereupon the venous pressure rose to 75 mm. of mercury and the blood flow increased to about 280 c.c. a minute. This was an increase of $2\frac{1}{3}$ times the normal blood flow in the iliac artery. The tourniquet pressure was then raised to 120, which equaled the systolic blood pressure of the animal. Immediately after this increase the venous pressure rose to 83 mm. of mercury, but there was a rapid decrease in the arterial blood flow to the extremity (from 280 c.c. a minute to about 180 c.c. a minute). This was presumably because the high tourniquet pressure interfered with the arterial inflow. The tourniquet around the thigh was then completely released, and the venous pressure dropped back to the normal level of 5 mm. of mercury. The arterial blood flow first decreased to 90 c.c. a minute for about 20 seconds, and then returned to 120 to 125 c.c. a minute, which was practically the same volume flow as was recorded before the tourniquet had been applied. A continuous record of this experiment on one of the dogs is shown in Fig. 8B.

Series 6. The Effect of Venous and Arterial Occlusion on the Blood Flow Through the Iliac Artery of the Unanesthetized Dog.—The following experiments were carried out on one animal. A blood flow unit was placed on the right iliac artery, under aseptic precautions, using ether anesthesia. The animal was allowed to recover, and the following day he was brought to the laboratory and blood flow studies were made without anesthesia. One-half grain of morphine was given subcutaneously because the animal was restless and not well trained. There was considerable fluctuation in the normal blood flow level, depending on his emotional state, but for the most part it remained between 100 and 200 c.c. a minute. This rather low volume flow is to be accounted for partly by the fact that the deep femoral artery, which lay distal to the blood flow unit, was ligated at the operation.

First a pneumatic venous tourniquet was applied to the thigh, and the blood flow was measured before, during, and after the application. Reference to the record of this experiment (Fig. 9) shows that, when the normal blood flow was varying from 200 to 80 c.c. a minute, the application of the tourniquet increased the arterial inflow to approximately 400 c.c. a minute. This increase in arterial flow was maintained for the duration of the venous occlusion. There was some fluctuation in the flow which was associated with the restlessness of the animal. After

the release of the tourniquet, the arterial inflow quickly returned to about 150 c.c. a minute.

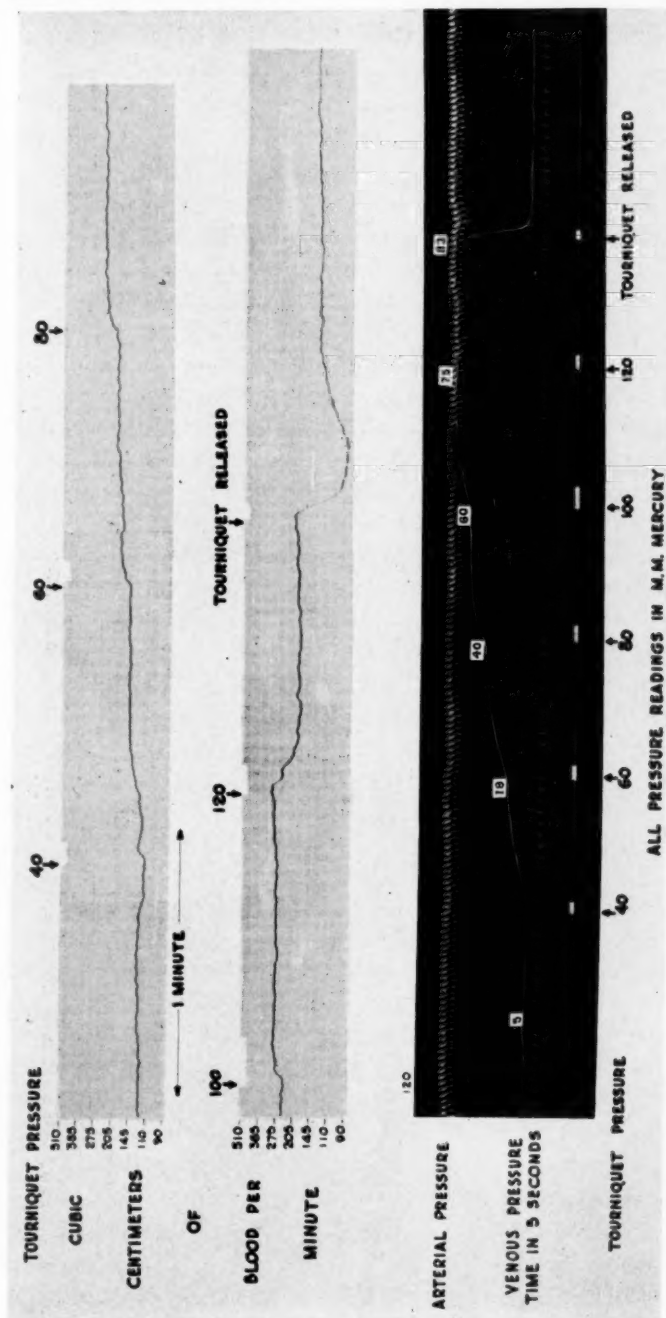


Fig. 8B.—The effect on the iliac artery blood flow of increasing venous pressures by means of a pneumatic tourniquet, applied to the thigh. It is to be noted in this record that, with each increase in the venous pressure of the extremity by raising the pressure in the tourniquet, there was an increase in the arterial blood flow until the venous pressure reached a level above 75 mm. of mercury. It will be seen that the venous pressure can be elevated much higher by this means than by ligation of the main vein of an extremity. The blood flow was increased by this means from 115 c.c. a minute to 280 c.c. a minute, whereas obstruction of the iliac vein in the same animal produced a rise from 115 c.c. a minute to only 215 c.c. a minute.

Then the femoral artery in the upper part of the thigh was occluded by digital compression (Fig. 9). It will be seen that this caused a

marked decrease in the volume flow through the iliac artery (from an average of 200 c.c. a minute to 45 c.c. a minute). This marked fall in arterial blood flow would be expected because of the fact that the deep femoral artery had been ligated at the time of operation, thus

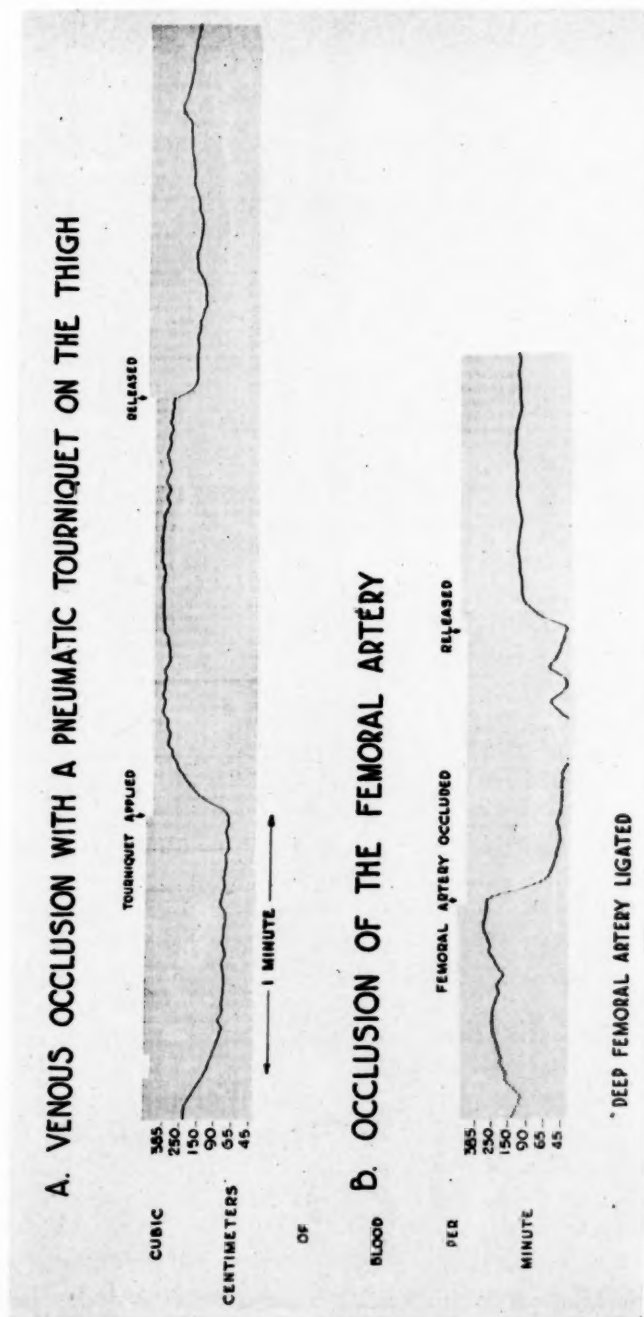


Fig. 9.—The effect of venous and arterial occlusion on the blood flow in the iliac artery of an unanesthetized dog. Note that venous occlusion with a pneumatic tourniquet and obstruction of the femoral artery produced the same effect as when the animal was under sodium amylal anesthesia. Compare these records with those in Fig. 7.

leaving a relatively small flow of blood in the iliac artery after occluding the femoral. The artery was released after one minute, and the arterial flow returned immediately to approximately 103 c.c. a minute. From this experiment it is readily seen that venous occlusion and arterial occlusion, without anesthesia, produced the same effects on the arterial inflow to an extremity as those which occurred under sodium amytal anesthesia.

DISCUSSION

Additional evidence concerning the therapeutic effect of venous occlusion on the arterial inflow to an extremity has been presented. This was obtained by means of a perfected thermostromuhr, with which it is possible to measure accurately the minute volume of blood passing through an artery or vein. Our investigations indicate that therapeutic venous occlusion does increase the arterial inflow to an extremity. By studying the blood flow in one extremity while venous occlusion was produced in the contralateral one, it was shown that the increase in the arterial blood flow is probably not caused by a humoral or nervous mechanism. However, further studies are needed to substantiate this view.

The effect of venous occlusion was found to be essentially the same, regardless of whether the arterial inflow was normal or deficient. The only difference was that, in the latter instance, the increase in the arterial blood flow developed more slowly. The effect of occlusion at various levels, by occluding, in the following order, the femoral and external and common iliac veins was studied. Simultaneous venous pressure records were made, and it was found that the increase in arterial inflow was directly related to the level of venous pressure. This was further corroborated by placing a pneumatic tourniquet around the thigh, and raising the venous pressure in steps by increasing, at intervals, the pressure in the tourniquet. By this means it was found that the arterial inflow increased with each increase in the pressure of the tourniquet until the level of the animal's systolic pressure was reached, at which point there was a falling off in the arterial blood flow despite a further increase in venous pressure. The paradox of having blood still flowing through the artery when the tourniquet pressure stands at the same level as the systolic pressure is explained by the fact that the thigh of a dog is uneven and oval, which makes it difficult to completely occlude the arterial blood supply by a pneumatic tourniquet unless very high pressures are used.

In the same animal, a comparison was made of the effect of occlusion of the common iliac vein, which carries most of the blood from the leg, with that produced by placing a pneumatic tourniquet about the thigh. It will be noted that after occlusion of the vein, the arterial inflow increased from 115 c.c. to 210 c.c. per minute, and that the venous pressure rose from 5 mm. of mercury to 25 mm., whereas, by means

of the pneumatic tourniquet, it was possible to raise the venous pressure from 5 mm. to 75 mm. of mercury, with a resulting increase in the arterial inflow from 120 c.c. to 280 c.c. a minute. These experiments indicate that producing venous occlusion by means of an adjustable pneumatic tourniquet increases the arterial inflow to an extremity to a greater degree than ligation of the main vein from the leg.

Since it is possible to increase the arterial inflow to a normal extremity after acute occlusion of its main arterial trunk, it seems justifiable to assume that, in chronic obliterative vascular disease, also, it can be increased by the same means, providing a certain amount of blood is reaching the extremity through collateral vessels. Thus, it appears most probable that the improvement in the circulation in the extremities of patients with obliterative arterial disease who have been treated with intermittent venous occlusion is to be at least partially explained by an increase in the arterial inflow during the period of venous occlusion. Reactive hyperemia apparently plays a minor role, if any, since it has been shown that the arterial blood flow returns very quickly to the preocclusion level after release of the tourniquet. For these reasons, it is recommended that, in the employment of intermittent venous congestion for the treatment of arterial insufficiency, a cycle in which the period of occlusion is longer than the period of release be used.

It is interesting to speculate on the mechanism of the increase in arterial inflow caused by venous occlusion. The following hypothesis, which is based on the foregoing experiments, is offered. The first effect of venous occlusion is to produce engorgement and dilatation of the veins. Next, dilatation of the venules, the capillaries, the arterioles, and the arteries occurs, in this order. This permits more blood to enter the vessels of the extremity because the increase in their diameter reduces resistance. In support of this view we have the original observations of Lewis and Grant,²⁰ who noted that venous occlusion increased the magnitude of the arterial pulsations. Additional evidence in favor of the above hypothesis is to be found in the experiment reported in Series 5 of this paper. There it was noted that the degree of increase in arterial inflow was directly related to the level of the venous pressure in the limb distal to the point at which the tourniquet was applied. Thus, it is suggested that the actual increase in arterial inflow comes about through this dilatation of the vascular tree. The higher the venous pressure, within certain limits, the greater the distention of the blood vessels which will result. Because of the enlargement of the blood channels, the peripheral resistance, despite the back pressure caused by the application of the tourniquet, is reduced; this permits a greater amount of blood to be forced through the vessels by the constant head of pressure on the arterial side. A diagrammatic sketch of this mechanism, produced by therapeutic venous occlusion, is shown (Fig. 10). Another possibility is that arteriovenous shunts may be

opened by the increased venous pressure, and so play a role. Other studies, which will be reported at a later date, are planned in an attempt to prove or disprove the above hypothesis.

CONCLUSIONS

1. Therapeutic venous occlusion increases the arterial blood flow to an extremity.
2. The arterial inflow to a limb can be increased to a greater degree by means of a pneumatic tourniquet placed on the thigh than by occlusion of the main vein.
3. The increase in blood flow bears a direct relationship to the height of the venous pressure up to a certain level, above which the arterial inflow begins to decrease.

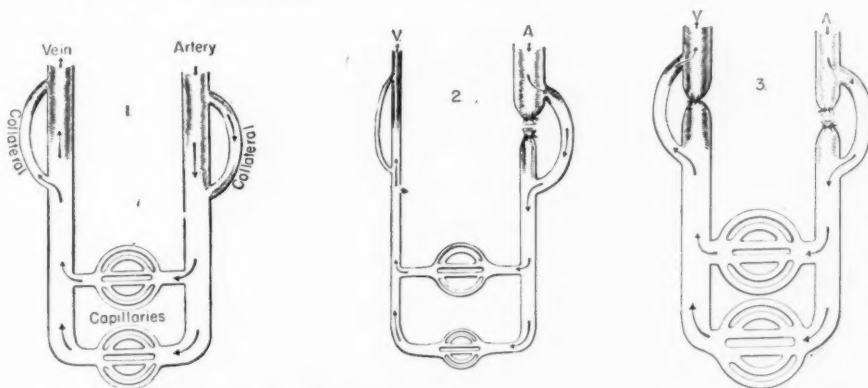


Fig. 10.—A schematic diagram showing the therapeutic effect of venous obstruction following acute arterial occlusion. 1, Normal artery, vein, capillaries, and collateral blood vessels; 2, the effect of ligation of the main artery, showing the decrease in size of the blood vessels distal to the ligature, indicating a decrease in arterial inflow to the limb; 3, the therapeutic effect of venous occlusion, showing dilatation of all of the vessels and capillaries, with a resulting increase in arterial inflow.

4. This study suggests that the benefit, in part, at least, which is derived from intermittent venous congestion in peripheral arterial insufficiency is a result of the increase in arterial blood flow which occurs during the period of congestion, rather than after the release of the tourniquet.

5. For this reason, in the treatment of arterial occlusion by intermittent venous congestion, it is recommended that the period of venous obstruction be longer than the period of release.

6. An explanation of the increase in arterial inflow to an extremity which is produced by therapeutic venous occlusion is suggested.

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DISCUSSION

DR. HERMAN E. PEARSE, Rochester, N. Y.—I should like to take this opportunity of pointing out the importance of Dr. Linton's observations. It has been known

for years, particularly from the work of Makins, Holman, Barney Brooks, and others, that vein ligation following sudden arterial occlusion would reduce the incidence of gangrene. It was shown by Rous that capillary permeability was increased during these periods of venous occlusion. It has been observed that the arterial bed is richer some weeks after venous occlusion. It has never been shown that the actual arterial inflow is increased in the presence of venous occlusion, and this morning we have seen very satisfactory evidence that it is.

This has therapeutic repercussions. Years ago I reported cases of vein ligation in the presence of arterial occlusion with satisfactory therapeutic results. We have means of intermittent or constant venous occlusion, and I believe that now we have a more rational basis for such therapy.

I should like to point out that, if it is true that the increased flow is caused by decreased resistance, then there must be other factors present, because the animals were under anesthesia. It is well known that anesthesia will remove any sympathetic vasospastic effect, so that there should be other mechanical factors in addition to this.

DR. NORMAN E. FREEMAN, Philadelphia.—I am really delighted to see this experimental work which confirms a clinical impression. If we observe the skin temperature of patients with thrombophlebitis, there is generally a higher skin temperature on the affected side. If the skin temperature is higher, that would indicate that there is an increase in arterial inflow, provided the blood is not simply shunted from the deep into the superficial venous system. With increased inflow there must be an increase in outflow, too, so that it is likely that there are collateral venous channels which are able to take the increase in the arterial inflow.

As far as the mechanism is concerned, Dr. Linton has suggested that it is purely mechanical, that is, that the back pressure on the veins causes dilatation which is then transmitted to the capillaries and to the arterioles, allowing larger inflow from the artery. A mechanical explanation is possible, but I do not think it is the entire story. The observations made by Lewis and Grant ten years ago on reactive hyperemia may throw some light on the mechanism of the increase in arterial inflow as the result of venous occlusion. They found that they could produce a reactive hyperemia in the tissues by venous obstruction, even temporary venous obstruction. Reactive hyperemia they considered as the repayment of a blood flow debt. The metabolism of the tissues continues unchanged, and with any deprivation of circulation some factor is produced in the tissues which causes a vasodilatation, so that for any degree of obstruction of inflow there is a compensatory increase afterwards.

It seems possible to interpret Dr. Linton's observations as indicative of a decrease in the supply of blood to certain tissues of the limb during the period of venous occlusion. During this period a chemical factor is released which will cause dilatation of the arteries.

This is a splendid piece of work and gives us some objective evidence to show the influence of venous occlusion on blood flow.

DR. NATHAN D. WILENSKY, Brooklyn.—I wish to thank Dr. Linton for his excellent presentation, and particularly for his beautiful experimental confirmation of the clinical observations which Dr. Collens and I have made on the use of intermittent venous occlusion in the treatment of peripheral arterial diseases.

We have always felt, just as Dr. Linton has so clearly demonstrated, that two factors play a part in the therapeutic value of intermittent venous occlusion. They are, first, the fact that during venous occlusion there is an increase in the rate of flow of blood through the major arterial pathways, and, second, and equally as important, is the increase in venous pressure which results in an increase in capillary pressure, thus favoring the diffusion of nutritional components through

the capillaries into the cells. This second phenomenon has, of course, been excellently presented by Landis in his studies on capillary pressure.

Although Dr. Linton did not observe reactive hyperemia with the release of venous occlusion, the work of Lewis and Grant still remains significant. If their observations are correct, there is a third, basic, physiologic factor which is partly responsible for the therapeutic value of intermittent venous occlusion. Just as Dr. Freeman has emphasized in his discussion, reactive hyperemia must be given time to come into play. It usually occurs about fifteen seconds after releasing the pressure, and its full effect may be observed for as long as two minutes.

Again I wish to say that I feel that Dr. Linton has made one of the most important contributions to the therapy of peripheral arterial diseases.

DR. LINTON.—I should like to say a word in reference to Dr. Pearse's remark about anesthesia. When operating on an animal under sodium amytal anesthesia, if one traumatizes the artery to the slightest degree, it becomes markedly constricted, whereas, if ether anesthesia is used, this does not occur. Thus, the barbiturates probably do not interrupt the sympathetic vasoconstrictor pathways.

I think the chief effect of venous occlusion is obtained during the period of occlusion because of the fact that the increase in arterial blood flow occurs at this time, and decreases as soon as the venous occlusion is released. I recently had a case in which I had to ligate both the external and internal iliac arteries in removing a large ovarian tumor, with the result that there was very little blood going into the limb. Following the operation I instituted intermittent venous congestion therapy, with nine minutes of occlusion and one minute without. It was by this means that I was able to get blood into the limb. Within two weeks and a half the patient was able to walk out of the hospital. It would seem that this case bears out my opinion that the chief benefit is derived during the period of occlusion, rather than following release of it.

STUDIES ON PERIPHERAL BLOOD FLOW

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SINCE the beginning of our work on blood flow in animals about ten years ago, we have investigated many problems concerning the peripheral circulation of the dog. In this report a number of studies have been summarized, and, in some instances, additional data only recently obtained have been included. These studies will serve to illustrate the dynamic nature of the peripheral circulation, as reflected in the blood flow in the femoral artery or vein.

TECHNICAL CONSIDERATIONS OF THE THERMOSTROMUHR

Since many readers may not be familiar with the thermostromuhr method of Rein or the direct-current thermostromuhr, it seemed advisable to devote the first part of the report to certain technical considerations.

In the preceding paper¹ on this program, studies on blood flow were described in which the Rein² thermostromuhr was used. Originally we made use of this method, but, after a careful analysis of certain thermal quantities, a thermostromuhr similar in principle was developed, in which diathermy plates were replaced by a direct-current heater. The modified method has all the advantages of the Rein technique, but has eliminated some of the disadvantages thereof, namely, the use of a high-frequency current and measurement of high-frequency resistance.

The fundamental principle underlying the Rein technique is illustrated schematically in Fig. 1. The high-frequency current is passed between the diathermy plates, heating the blood vessel and the blood. However, most of the heat is developed in the wall of the blood vessel, and this, in turn, affects the differential thermocouple, giving a definite relationship between the flow of blood and the deflection of the galvanometer. Fig. 2 shows the construction of a direct current thermostromuhr³ with a heater, and a differential thermocouple as in the Rein unit.

The similarity of response of a high-frequency current unit and a direct-current unit is shown in Fig 3. This record was obtained by perfusing blood through a blood vessel. Note that the times required to bring the two units into equilibrium are practically identical.

When the deflections of the galvanometer and the corresponding flows are plotted on rectangular coordinate paper, the curve is a hyperbola for the usual range of flow. These data are obtained from records similar to those of Fig. 3, and are plotted on logarithmic paper (instead

Received for publication July 20, 1940.

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of rectangular coordinate paper) because the straight line is more convenient for checking subsequent calibrations for a given unit than a curve would be. The method requires careful calibrations for each unit before quantitative observations on blood flow in situ can be made. The question is often asked: "What effect does the thickness of the wall of the blood vessel have on the calibration curve?" We can answer this best by saying that calibrations on veins correspond to calibrations on arteries. We have units for which calibrations have remained relatively the same for a period of two and a half years when the calibrations have been made with veins as well as with arteries.

The reliability of the thermostromuhr has been checked in various ways. Recently, a type of flowmeter has been constructed in which the same principle is used as that which is employed in the thermostromuhr. The flowmeter consists of a bakelite tube which is inserted into the blood vessel by cannulation. This procedure, of course, necessitates the use of an anticoagulant. Nevertheless, it can be used simultaneously with the thermostromuhr on the same artery in situ for the purpose of checking results. Table I shows the results of such an experiment.

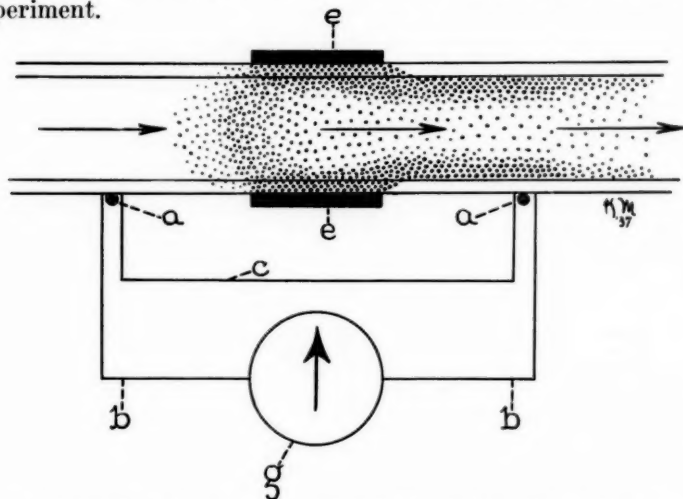


Fig. 1.—Schematic drawing of a diathermy-thermo-element applied to a blood vessel. *e, e*, Platinum electrodes; *a, a*, thermojunctions; *c, c*, constantan wire; *b, b*, copper wire; *g*, galvanometer. Arrows indicate direction of flow of blood.

Technically, we are able to measure blood flow with an error of no more than 10 per cent when the flow is not turbulent. The units can be applied aseptically while the experimental animal is under the effects of anesthesia. After recovery of the animal from the operation, blood flow may be measured for an indefinite time.

PHYSICAL FACTORS THAT MODIFY BLOOD FLOW

Generally speaking, the flow of blood in a given blood vessel is proportional to the average blood pressure and inversely proportional

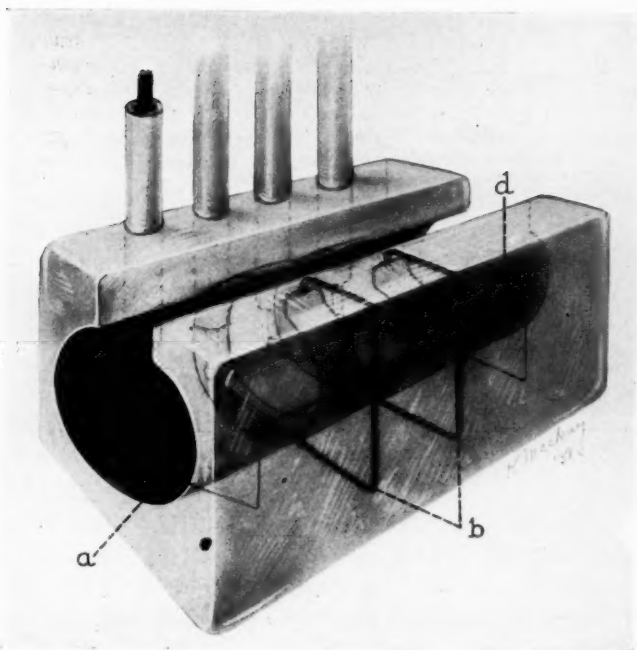


Fig. 2.—A thermostromuhr unit with direct-current heater. One of the thermo-junctions shown, at *a*, is made by soldering copper wire (0.0016 inch) to a constantan wire (0.002 inch) which is embedded in the groove *d*. The heating unit *c* consists of a folded loop of nichrome wire rolled into ribbon form and soldered to copper wires *b*.

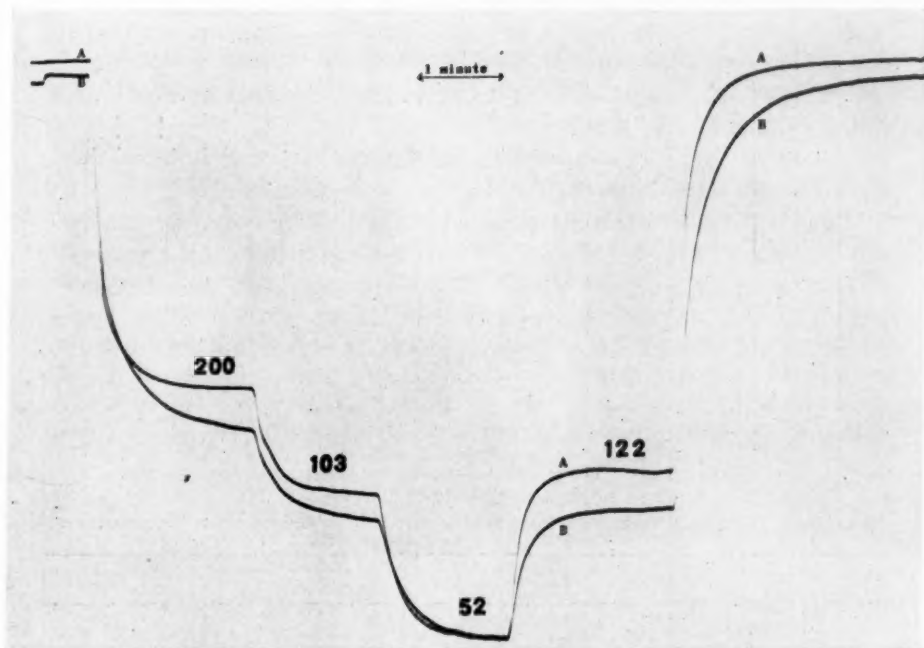


Fig. 3.—A comparison of the thermal equilibrium curves for the high-frequency unit (*A*) and the direct-current unit (*B*). The figures give the blood flow in cubic centimeters per minute. The deflection for each flow is the distance from the zero line to the horizontal portion of the curve.

TABLE I

A COMPARISON OF BLOOD FLOWS, AS MEASURED BY THE THERMOSTROMUHR, WITH THOSE RECORDED SIMULTANEOUSLY WITH A FLOWMETER

BLOOD FLOW (C.C. PER MIN.) IN CAROTID ARTERY	
BY THERMOSTROMUHR	BY FLOWMETER
187	205
210	227
245*	288
265	260
240	238
225	229
225	212
144	155
153	165
260	248

*Equilibrium not fully established because of sudden fluctuation in blood flow.

to peripheral resistance. Hence, if the increase in average blood pressure is accompanied by an increase in peripheral resistance, there may be no alteration in flow. From observations of blood pressure alone, no conclusions may be drawn regarding changes in the flow of blood in any given vessel. Obviously, this is true when the various factors of the vasomotor system that maintain or regulate blood pressure are considered.

Similarly, a consideration of the velocity of blood flow does not provide an insight into values for the volume flow of blood unless the size of the cross section of the blood vessel can be ascertained. It might be well to point out the fact that the maximal velocity of laminar flow in tubes, blood vessels, and the like, is twice the average velocity and, consequently, that it is difficult to correlate "circulation time" with actual volume flow of blood.

Continuing the discussion of physical factors that modify blood flow, there is one factor in particular that we wish to emphasize; it is one that seems to have been misinterpreted in the past, namely, the relationship of reduction in the size of the lumen of an artery to the capacity of that vessel to transport blood. This factor has been investigated in vitro and in vivo, and with constrictive devices situated either inside or outside the vessel.⁴ Table II shows the effect of introducing a bakelite

TABLE II

EFFECT ON THE BLOOD FLOW OF INTRODUCING CONSTRICTING UNITS (8.0 MM. LONG) INTO AN ARTIFICIAL CIRCULATORY SYSTEM AND INTO THE CAROTID ARTERY OF AN ANESTHETIZED, HEPARINIZED DOG. (THE ORIGINAL DIAMETER OF THE LUMEN IS 3.00 MM.)

PER CENT DECREASE IN		PER CENT DECREASE IN BLOOD FLOW		
DIAMETER	AREA	GRAVITY SYSTEM	DALE-SCHUSTER PUMP SYSTEM	ANIMAL SYSTEM
17	31	2	0	0
35	58	7.5	0	5
48	73	17	4.5	18
54	79	30.5	20	24
67	89	58	49	44.5
80	96	88.5	79	71

constrictive device 8 mm. long *into* a blood vessel. If the size of the lumen is reduced from 3 to 1 mm., thereby reducing the effective area of cross section to 11 per cent, the blood flow will still remain more than one-half of what it originally was. Similar results were obtained when the lumen of the blood vessel was reduced by placing constrictive devices on the outside of the vessel.

BLOOD FLOW IN THE EXTREMITY IN THE TRAINED DOG

The studies on peripheral circulation reviewed under this title include those which were carried out under natural conditons. No operation except that necessary for the application of the thermostromuhr was performed and no drugs were injected. These studies serve as a contrast to those to be discussed later, in which natural conditions have been altered by the investigators.

Rhythmicity.—Our interest in rhythmic variations in blood flow was aroused by two independent studies which were being conducted at about the same time. One of us (BalDES) was studying the blood flow to the finger by means of a plethysmograph. The photographic records made during this study showed rhythmic variations of considerable magnitude in a resting man. An intensive study of the blood flow in the spleen⁵ of the trained dog was the other investigation in progress at this time. The flow was measured by the thermostromuhr method. The well-known "splenic rhythm" was present in almost all of the records of blood flow, and was particularly pronounced following a sudden noise or an intravenous injection of epinephrine. This "splenic rhythm" was studied by recording, simultaneously, the volume of the spleen, the flow of blood in both splenic artery and splenic vein, and the blood pressure. We concluded that the rhythm was not caused by rhythmic contractions of the splenic musculature or by variations in systemic blood pressure, but, rather, by rhythmic variations in the vascular bed. In an attempt to determine the cause of this rhythmicity, a careful study was made of the phenomenon in the extremities of the dog. Blood flow was measured in the femoral artery, and the volume of the leg was recorded by means of a very sensitive plethysmograph. Simultaneously, the mean blood pressure and respiration were also noted. The rhythmic variations in volume of the leg paralleled those in blood flow, but were usually independent of blood pressure and respiration.

Fig. 4 shows the rhythmic variations in the flow of blood in the femoral artery, and indicates the difficulty which may be experienced in determining the normal or basal flow. This record was made on a trained dog, and shows the comparison between variations in blood flow, as indicated by the thermostromuhr, and the changes in volume, as recorded by a plethysmograph.

Exercise.—The effect of exercise on the flow of blood to the muscle is well known. Actual quantitative observations on the flow in the femoral or common iliac artery, as well as in other blood vessels, of the

trained dog have been made during natural exercise of the animal and recorded photographically while the dog was walking on the treadmill at the rate of three miles per hour.^{6, 7} The flow increases immediately at the onset of exercise. The results of a series of experiments are shown in Table III.

TABLE III
EFFECT OF EXERCISE ON BLOOD FLOW

DOG	WEIGHT (KG.)	ARTERY	BLOOD FLOW (C.C. PER MIN.)		
			CONTROL	DURING EXERCISE*	AFTER EXERCISE
1	18.4	Femoral	99	410	168
2	11.6	External iliac	58	295	86
3	14.4	Common iliac	215	995	262
4	17.8	Common iliac	184	735	232
5	15.0	Common iliac	235	935	420
6	20.6	Common iliac	305	1000	328
7	12.2	Femoral	147	498	193

*Walking on horizontal treadmill at 3 miles per hour.

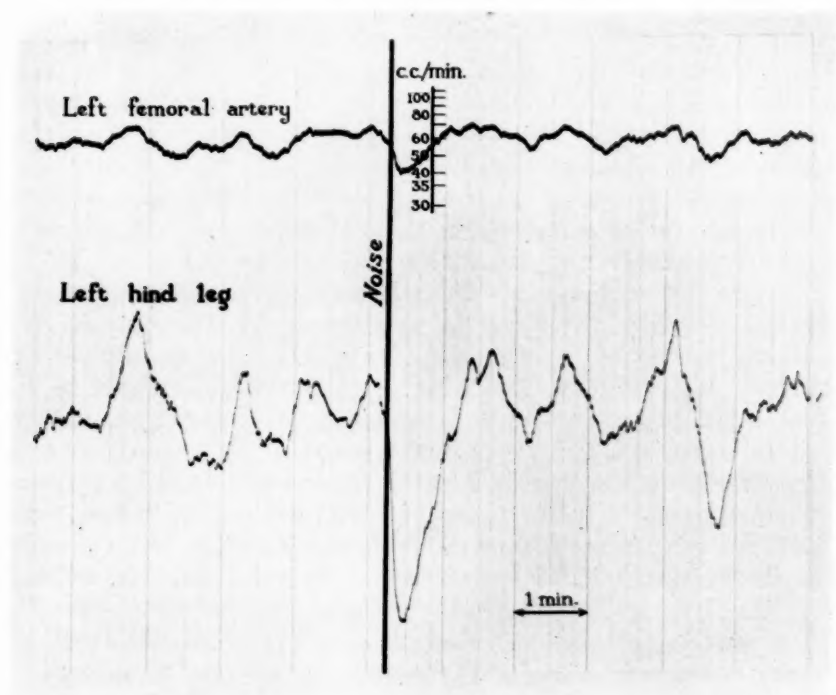


Fig. 4.—Rhythmic variations in the flow of blood in the left femoral artery and in the volume of the left hind leg.

Meals.—An extensive study of the effect of meals on the flow of blood has been made, part of which has been published.⁸ We found that there was a definite increase in blood flow in every vessel which we studied following the ingestion of food. The maximal increase was frequently

as great as 100 per cent. Fig. 5 shows the typical results of observations on the femoral artery. These results were contrary to previously existing opinions, which had been developed on the basis of indirect evidence. They were confirmed in the human being by Burton and Murlin,⁹ who used the Thermal Circulation Index for indicating blood flow.

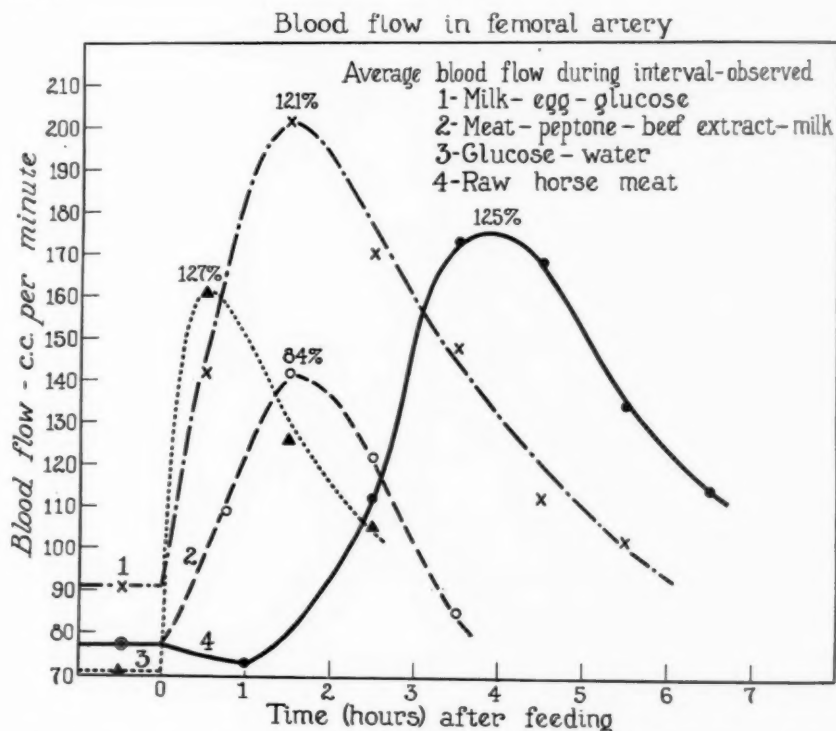


Fig. 5.—The effect of meals on the blood flow in the femoral artery of the dog.

BLOOD FLOW IN THE EXTREMITY UNDER ALTERED CONDITIONS

Anesthetic Agents.—The flow of blood in the femoral artery is increased markedly during surgical anesthesia induced by ether. At the same time, the blood pressure either remains the same or is increased slightly. Our first observations on the effect of lumbar sympathectomy on the femoral blood flow were made while the experimental animals were under the effects of ether anesthesia, and we failed completely to detect any effect caused by unilateral removal of the entire sympathetic chain from the level of the second lumbar vertebra. We suspected that the failure to detect any change in flow was referable to the anesthetic agent employed. This failure to detect the effect of sympathectomy on the blood flow in the femoral artery marked a turning point in our investigations on the flow of blood. A unit that could be sterilized by boiling was constructed, and all subsequent studies, when desired, have been made on trained dogs.

Sympathectomy.—After establishment of the fact that the simultaneous blood flow in both femoral arteries is approximately the same under resting conditions in the trained dog, unilateral sympathectomy

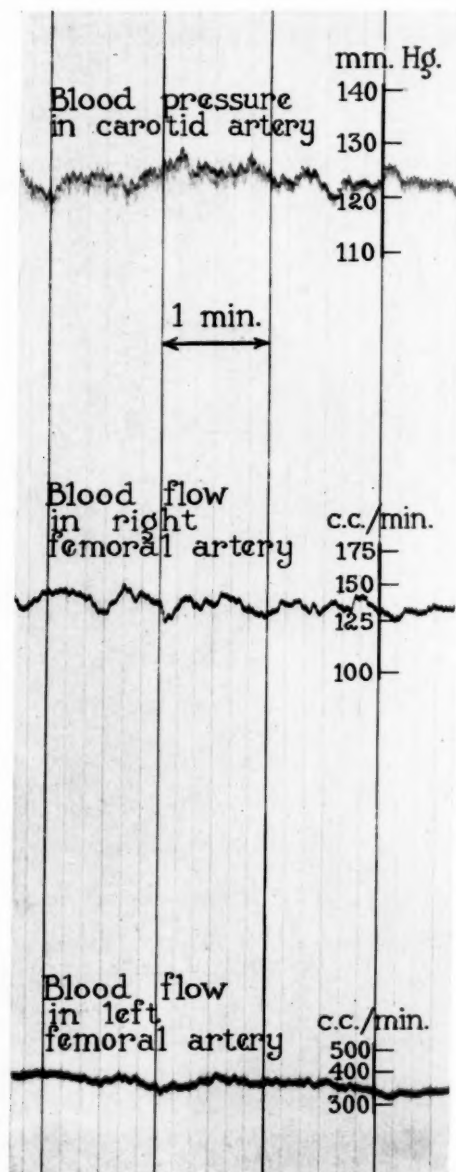


Fig. 6.—Simultaneous measurement of mean blood pressure in the carotid artery and of the blood flow in both femoral arteries in a dog which has undergone left lumbar sympathectomy. Note the vasomotor influence causing variations in flow in the artery on the innervated side.

was performed. When the dog had recovered from this operation, a comparative study of the flow in the two femoral arteries was made;

the units were applied while the animal was under the effects of a procaine type of anesthetic agent (pontocaine hydrochloride), administered by local infiltration. The blood flow in the artery on the denervated side was about double that on the innervated side.¹⁰ This effect has persisted as long as two years and ten months. This marked difference in flow promptly disappeared when the animal was anesthetized with ether.

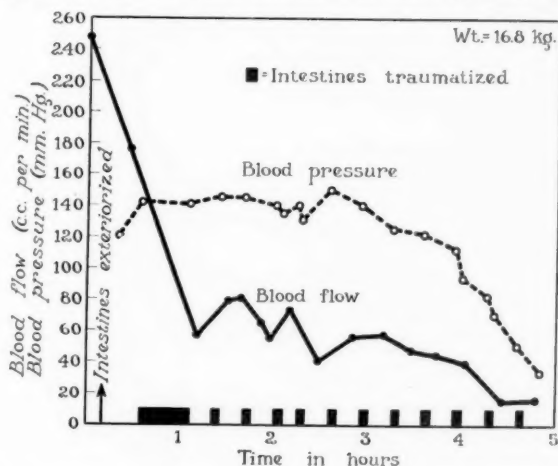


Fig. 7.—Results of a typical experiment in which shock was produced by manipulation of the intestines.

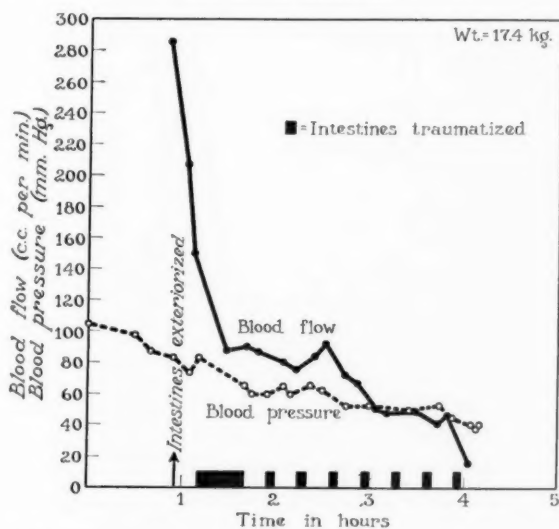


Fig. 8.—Results of experiment similar to that represented in Fig. 7, on a different animal.

Fig. 6 shows a record of blood flow in both femoral arteries, recorded simultaneously with mean blood pressure in the carotid artery, of a trained dog on which left lumbar sympathectomy had been done nine months previously. This record gives the necessary data for calcula-

tion of the index of peripheral resistance in each femoral artery, that pressure is, ———. The index of peripheral resistance in the femoral artery flow

on the innervated side is about two and a half times that in the artery on the denervated side in this particular experiment.

Traumatic Shock.—In the production of shock by manipulation of the intestines, the flow of blood in the femoral artery is reduced markedly and rapidly. The blood pressure may be maintained for some time above what might be considered a good physiologic level. Finally, after successive manipulations of the intestines at intervals, the blood pressure reaches a shock value; the flow of blood in the femoral artery decreases more markedly; and the dog dies shortly thereafter. Figs. 7 and 8 illustrate these results.

Thyrotoxicosis.—If dogs are fed desiccated thyroid gland or are given thyroxine, symptoms of thyrotoxicosis develop. In the presence of this condition, the flow of blood in the femoral artery may be increased threefold.¹¹

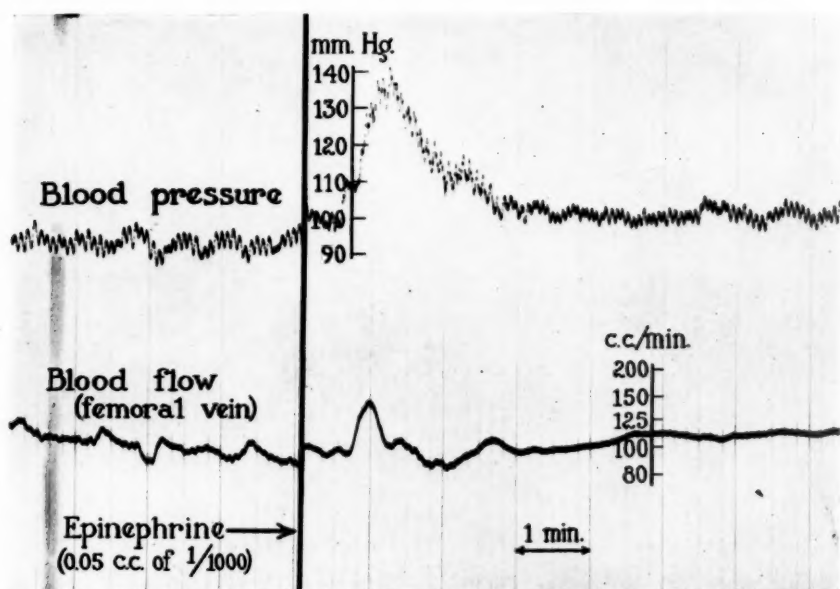


Fig. 9.—The effect of an intravenous injection of 1:1,000 solution of epinephrine (0.05 c.c.) on the blood flow in the femoral vein and on the mean blood pressure in the carotid artery of the trained dog.

Drugs.—The effect of intravenous injections of, say, 0.05 c.c. of a 1:1,000 solution of epinephrine is not always the same on the flow of blood in the femoral blood vessels. The result may be an increase, a decrease, or no significant change, according to the resultant effect of the various factors controlling blood flow. The change in blood flow

referable to epinephrine is very transient. Fig. 9 illustrates an effect produced on the flow of blood in the femoral vein and the blood pressure in the carotid artery.

Pressor and Diuretic-Antidiuretic Principle of Posterior Lobe of Pituitary Body (Pitressin).—When pitressin is administered subcutaneously or intramuscularly, it exerts no significant effect on the blood flow. However, if it is administered intravenously, its effects are the most dramatic of those of any drug that we have observed. The effect on every blood vessel which we have studied thus far is a *marked decrease* in flow. The flow in the femoral artery or vein decreases as much as 90 per cent, and remains decreased for several minutes, when 1 pressor

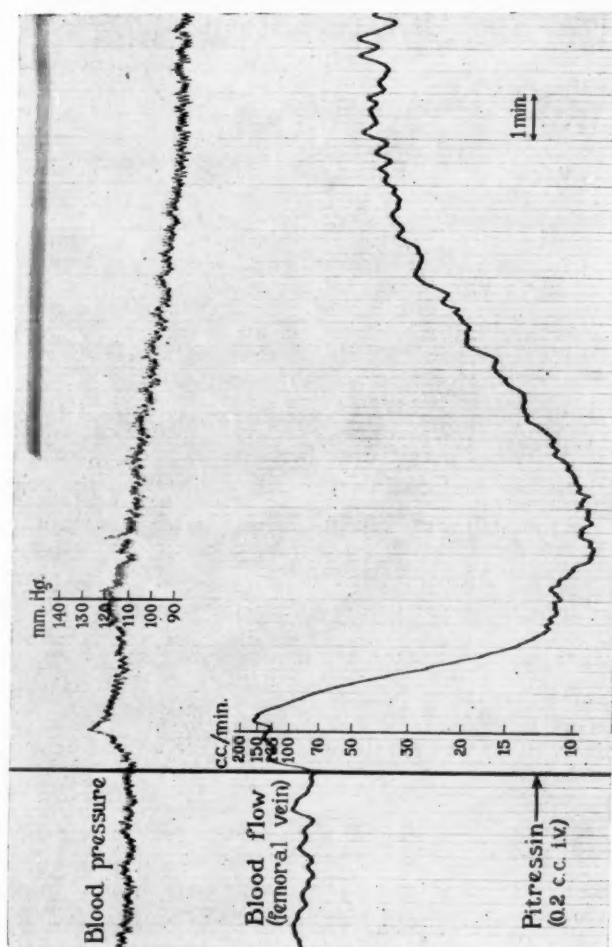


Fig. 10.—The effect of an intravenous injection of pitressin (0.2 c.c.) on the blood flow in the femoral vein and the mean blood pressure in the carotid artery of the trained dog.

unit is injected intravenously.¹² Frequently, the flow does not attain the preinjection value until sixty or more minutes have elapsed. The effect of pitressin is not entirely peripheral, for it is accompanied by a

marked slowing of the pulse rate and by either no increase or only a moderate increase in blood pressure. Fig. 10 shows a typical result of the injection of pitressin.

SUMMARY AND CONCLUSIONS

Using a thermostromuhr, we have been able to measure the flow of blood in large arteries or veins of the peripheral vascular system of the trained dog under various conditions. It is our hope that the data presented will serve to emphasize the fact that the blood flow to an extremity is influenced by many factors, any one of which, if altered, may profoundly affect the flow of blood to that region.

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DISCUSSION

DR. IRVINE H. PAGE, Indianapolis.—I think Dr. Baldes' observation on the blood flow after constriction of an artery is of great interest. We have all come to appreciate the work of this team of investigators. In applying Dr. Goldblatt's clamp to the renal artery and in applying similar clamps to the aorta, one is, I think, impressed by what tremendous constriction is required to reduce the blood flow. When one speaks of an "ischemic kidney" after applying a clamp, it should be remembered that the blood flow is not markedly reduced because of the strong constriction required to reduce the blood flow appreciably.

We have also noticed that, shortly after applying the clamp to a renal artery or the aorta, the vessel itself thins out under the clamp so that much more blood gets through than one might anticipate. In other words, the pressure against the clamp causes thinning within the clamp, allowing more room for the blood to get through.

DR. LOUIS N. KATZ, Chicago.—The Mayo group is to be congratulated on their excellent report on this important subject. It must be emphasized, as they have shown, that the blood pressure, blood flow, velocity of flow, and circulation time are not interdependent, but are independent of each other. One of these factors may change without affecting the others. Consequently, when investigating changes in the circulation, one must take care not to draw too many deductions regarding the other variables from a change in one.

The circulation in the peripheral vessels of the limb, as in any vessel, is complicated, and only by the application of methods and correlations such as those reported in this communication can our knowledge of the circulation in blood vessels be enhanced.

THE VASODILATING ACTION OF VARIOUS THERAPEUTIC PROCEDURES WHICH ARE USED IN THE TREATMENT OF PERIPHERAL VASCULAR DISEASE

A PLETHYSMOGRAPHIC STUDY

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IN VIEW of the conflicting reports as to the efficacy of the therapeutic agents commonly employed in the treatment of peripheral vascular disease, the vasodilating action of some of these procedures was investigated by means of the venous occlusion plethysmographic method. With this method the total blood flow to a portion of an extremity can be measured, and hence any alteration in flow produced by a drug or a procedure becomes apparent and can be expressed quantitatively.

METHOD

The study was performed upon thirty-one patients who were suffering from various types of peripheral vascular disease (chiefly thromboangiitis obliterans and Raynaud's disease), upon thirteen patients with various mental states (schizophrenia, mental deficiency), and upon thirty-four normal subjects. Some of the subjects were used for testing the effect of more than one drug. Blood flow measurements in c.c. per minute per 100 c.c. of limb volume were obtained according to the technique previously described.¹ The bath temperature (temperature of the water in the plethysmograph) was maintained at 32° C., and the room temperature between 25° and 27° C. The procedure which was generally followed consisted of placing a hand and a contralateral leg, forearm, or foot into plethysmographs, and recording control blood flow readings in two extremities for about a half hour. The drug was then administered by the appropriate route, or the procedure under study was begun, and blood flow readings were taken at 10-minute intervals for one to three hours, depending upon the rapidity with which changes in blood flow were observed. It was inadvisable to continue the test for more than 3½ hours because the subjects generally became restless beyond this point, which made further observations unreliable. The onset and duration of the various symptoms which resulted from the administration of the drugs were noted, and the blood pressure and pulse rate were recorded at intervals during the experiments.

RESULTS

Calcium Gluconate, "Padutin," Papaverin, "Spasmalgin,"
Thiamin Chloride.

Calcium Gluconate.—Weichsel² has recently reported that the intravenous injection of calcium gluconate in cases of peripheral occlusive arterial disease was followed by alleviation of pain and an increase in ability to walk. He concluded that the response was caused by the

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Aided by the Samuel and Regina Kuhn Fund and a grant from the Dazian Foundation for Medical Research.

Presented before the American Heart Association, June 8, 1940, New York, N. Y.
Received for publication July 24, 1940.

vasodilator effect of calcium on the parasympathetic or antisympathetic mechanism. Accordingly, we tested this drug on six subjects by injecting 2.75 Gm. intravenously and noting the effect upon the peripheral circulation. In five of the six subjects no change in blood flow was noted in the hand or leg, but in the remaining case the flow in the hand was approximately doubled, and remained elevated for about forty minutes.

Padutin.—The use of various tissue extracts in the treatment of peripheral vascular disease has been advocated by a number of authors.³⁻⁶ One of these substances, "Padutin," a deproteinized pancreatic extract, was found by Frenkel⁷ to dilate peripheral vessels and to increase their permeability. Werle and Multhaupt⁸ reported that, after intramuscular and intravenous injection of this substance, the skin temperature of the finger tips was elevated. We tested the vasodilator effect of "Padutin" by injecting 4 "biologic" units intramuscularly in a series of seven subjects. In no instance was a change in blood flow to either the hand, leg, or forearm observed over a period of 80 to 100 minutes following its administration.

Papaverin and "Spasmalgin."—Mulinos and his associates⁹ have recently reported that the intravenous injection of papaverin hydrochloride in cases of Raynaud's disease was followed by an increase in the rate of blood flow to the hand, as well as complete alleviation of the cyanosis and pain caused by exposure to cold. Littauer and Wright,¹⁰ however, concluded that this drug is less effective in causing vascular relaxation than immersing an extremity in warm water. We investigated the vasodilator effect of papaverin hydrochloride ($\frac{1}{2}$ grain) and the proprietary substance "Spasmalgin," which contains pantopon and atropine, as well as papaverin, upon seventeen patients who were suffering from either thromboangiitis obliterans, scleroderma, or hypertension. With both these substances there was either no change or only a slight increase in flow to the hand, except in one case in which the blood flow was doubled and remained elevated for about forty-five minutes. In the foot, very little response was observed in any of the experiments.

Thiamin Chloride.—Since thiamin chloride has been used with some degree of success in alleviating rest pain of ischemic origin,¹¹ it was thought of interest to ascertain whether or not this drug has any vasodilating properties. In a series of five subjects there was very little effect on the blood flow to the hand, leg, and foot after the intravenous administration of 10,000 to 20,000 units. In contrast with these observations was the effect of nicotinic acid,¹² which is another fraction of the vitamin B complex. In a series of fifteen normal subjects, the oral administration of 100 to 300 mg. of nicotinic acid produced a significant augmentation in flow to the hand and forearm, averaging 2.3 times the control level. The increased flow with a single dose lasted for approximately seventy minutes.

Generalized Effects.—The administration of "Padutin" and thiamin chloride was followed by no subjective symptoms, whereas with calcium gluconate a generalized feeling of warmth, together with a flushing of the face and neck, was usually experienced. Papaverin generally produced no symptoms or occasionally a fleeting headache; with "Spas-malgin," headache was much more common, and was associated with a sensation of dizziness. All four drugs had little effect upon blood pressure or pulse rate.

Alcohol, Stilbestrol, Prostigmine

Alcohol.—Since it is well known that alcohol causes a rise in skin temperature, particularly of the finger tips, and an increase in oscillations, it was decided to obtain a quantitative measure of the vasodilator effect in a series of seven subjects. Whiskey, in 60 to 80 c.c. doses, was given orally, and blood flow readings were taken for the subsequent 80 to 110 minutes. Fig. 1 shows a typical response; an increase in blood flow was generally observed in the hand (about two times the control level), and little or no effect in the leg or forearm. These observations are in accord with those of Silbert and his associates,¹³ who used skin and muscle thermocouples.

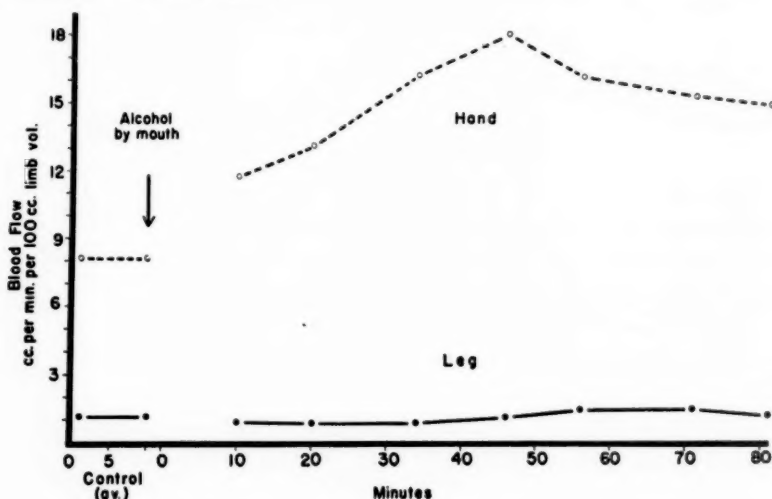


Fig. 1.—Effect of the oral administration of 60 c.c. of whiskey.

Stilbestrol.—Recently a number of reports have appeared advocating the use of the various ovarian and testicular hormones in the treatment of peripheral vascular disease of both spastic and organic types.¹⁴⁻¹⁶ Accordingly, stilbestrol, a synthetic estrogenic substance, was injected intramuscularly (10,000 international units) in a series of five female subjects. A significant increase in blood flow in the hand was observed in four subjects, whereas no change took place in the fifth subject. The maximal flow which was attained averaged 3.5 times the control level,

and the duration of the increase averaged seventy-five minutes. It is necessary to point out, however, that all of the subjects in this group had low control flow readings in the hand as a result of vasoconstriction of nervous origin. In all five instances there was no significant increase in flow in the forearm. In contrast with these results, estrin or theelin, in dosages of 2,000 international units, produced no change in blood flow to either the hand or forearm.

Prostigmine.—The fact that prostigmine has an inhibitory action upon choline esterase, thus permitting an unimpaired action of acetylcholine, led Perlow¹⁷ to investigate its effects upon the peripheral circulation. He found that a significant increase in the skin temperature of the digits and a definite acceleration of capillary blood flow resulted from the administration of this drug. We studied the effect of the intramuscular injection of 0.5 mg. and the oral administration of 15 mg. of prostigmine methylsulfate in a series of seven subjects. The flow in the hand in four instances showed an increase which ranged from 1.5 to 2.5 times the control level, but there was no change in the remaining three. In the forearm the flow was approximately doubled in two instances and unaffected in the remaining five.

Generalized Effects.—The administration of prostigmine induced no symptoms; stilbestrol and alcohol produced a feeling of warmth and some flushing of the face. Stilbestrol caused a fall in systolic blood pressure which averaged 10 mm. Hg., but the other three drugs had little effect in this respect.

HYPERTONIC SALINE SOLUTION, HISTAMINE

Hypertonic Saline Solution.—Silbert,¹⁸ Samuels,¹⁹ and others have advocated the use of large quantities of 5 per cent saline solution in the treatment of thromboangiitis obliterans. Friedlander and her co-workers²⁰ reported a definite increase in both the skin and muscle temperature of the lower extremities following its intravenous administration. We tested the vasodilating action of hypertonic saline solution (250 c.c.) on a series of twenty-one subjects, sixteen of whom had thromboangiitis obliterans; the other five were normal. During the period of injection (which generally lasted from twenty to twenty-five minutes), and for the subsequent 60 to 100 minutes, the blood flow in the hand was found to be unchanged or slightly increased in fifteen trials, and significantly increased in the remaining six. Fig. 2 is typical of the response when there was an augmentation in flow in the hand. In the leg, which was tested five times, there was either no change or a slight increase in two trials, and a definite increase in the remaining three. In the foot, during the period of injection, there was either no change or a slight increase in flow in eight of fourteen experiments, and a significant augmentation in the remaining six. However, after the injection was completed the increased flow to the foot persisted in only three instances (for an average period of 80 minutes). Physiologic

saline, which was tested under similar conditions, had little or no effect upon blood flow through the hand and foot, even during the period of administration.

Histamine.—Kling and Sashin²¹ and others have reported excellent results with histamine iontophoresis in such conditions as Raynaud's disease, acroparesthesia, and thromboangiitis obliterans. The vasodilating effect of this drug, using the intravenous route, was investigated in a series of twelve subjects. From 0.3 to 0.5 mg. of histamine acid phosphate, dissolved in 10 c.c. of saline, was administered over a period of seven to ten minutes. In the hand, during the time of injection, there was a significant increase in flow (about two to three times the control level), which, in half of the trials, persisted for about fifteen to twenty minutes after the injection was completed. In the remaining instances the flow returned to the control level quickly. In the case of the leg there were marked variations in flow during the period of administration, and then a return almost immediately to the previous level (Fig. 3). It is obvious that these results cannot be compared with those reported by authors²¹ who employed iontophoresis.

Generalized Effects.—Hypertonic saline produced practically no symptoms except the occasional complaint of a feeling of thirst. Histamine generally caused a feeling of warmth and flushing of the face and a transient throbbing headache; these symptoms were for the most part limited to the period of administration. The latter drug generally caused an elevation of both systolic and diastolic blood pressure during the injection phase, but the pressure returned to the control levels almost immediately afterward (Fig. 3). In some instances, with histamine, a drop in pressure was observed during the period of administration. The pulse rate varied, but in no constant direction. With hypertonic saline solution, the blood pressure and pulse rate responses were slight and inconsistent.

INTERMITTENT VENOUS OCCLUSION

The procedure which has probably had the most extensive clinical trial in recent years in the treatment of peripheral vascular disease is that of intermittent venous occlusion. Collens and Wilensky,²² who popularized it, and other investigators, including Kramer,²³ Brown and Arnott²⁴ and de Takats and his associates,²⁵ regard this procedure as beneficial. On the other hand, Veal and McCord,²⁶ Allen and McKechnie,²⁷ Wright²⁸ and others believe that the value of the treatment has not been definitely established. The rationale of the method is based upon the work of Bier²⁹ and of Lewis and Grant.³⁰ According to the latter authors, the application to an extremity of pressures definitely below the level of systolic pressure produces a state of reactive hyperemia.

We tested the vasodilating action of such a procedure by intermittently applying a pressure of 70 mm. Hg (two minutes on and two

minutes off) for periods of two to three hours; blood flow measurements were made every fifteen minutes. Eleven subjects were used; five of them complained of intermittent claudication, and the remainder were normal. In no instance was a sustained increase in blood flow observed in the leg or forearm during or following this procedure. In the hand and foot, a slight increase occurred in three trials. Whether or not there was an augmentation in flow during the period in which the high venous pressure was maintained could not be ascertained by the

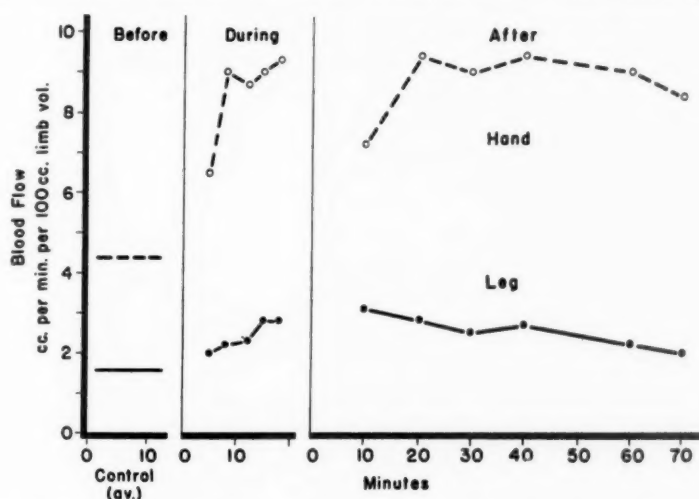


Fig. 2.—Effect of the intravenous injection of 250 c.c. of 5 per cent saline solution upon blood flow in the hand (dotted line) and leg (solid line).

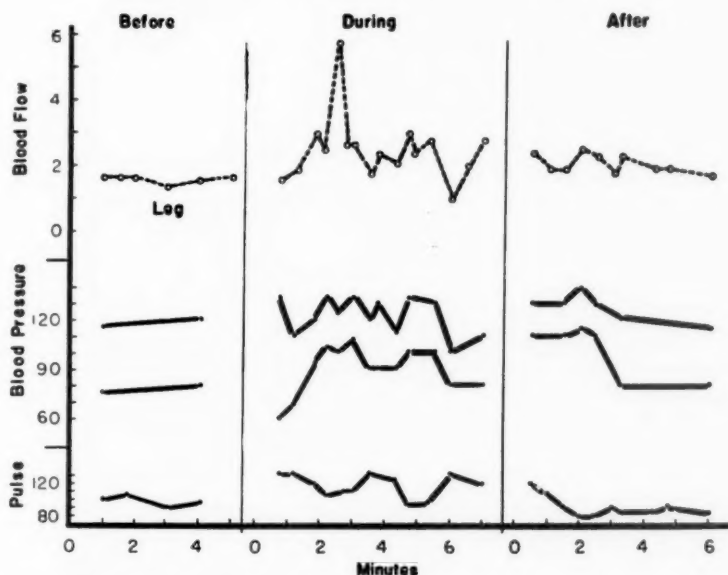


Fig. 3.—Effect of the intravenous injection of 0.35 mg. of histamine acid phosphate (dissolved in 10 c.c. of physiologic saline solution) upon blood flow in the leg, upon blood pressure, and upon pulse rate.

plethysmographic method. Linton, et al.,³¹ who used the thermotromuhr in experiments on dogs, have recently reported that the flow does accelerate during this period.

DISCUSSION

It would seem from the data presented that most of the drugs which were studied did not consistently produce a significant and prolonged augmentation of the peripheral circulation. Alcohol, stilbestrol, and histamine increased the blood flow to the hand, but not elsewhere, and hypertonic saline solution had a similar effect on the leg and foot, as well as the hand, but only in about one-third of the trials. In respect to intermittent venous occlusion, no sustained state of reactive hyperemia appeared to be produced by the procedure—at least as far as could be ascertained by the plethysmographic method.

The fact that some investigators have used the skin temperature thermometer and the oscilometer in their studies may account in part for the different conclusions as to the vasodilator action of the various drugs. For example, Popkin,³² who utilized both of these procedures, reported that nicotinic acid has either a slight effect, or none at all, upon peripheral blood flow. However, in a recent study¹² in which the plethysmographic method was used, it was found that this drug produced a significant and consistent increase in blood flow to the hand and forearm, although the skin temperature changes were similar to those reported by Popkin. Again, with massive doses of insulin,³³ very significant increases in blood flow to the forearm (four and five times the control level) were observed, whereas in some instances the forearm skin temperature actually fell during the period of accelerated blood flow. Of interest with respect to the relative value of the oscilometer is the case of a patient with multiple syphilitic aneurysms of the arch of the aorta which involved the orifices of the right innominate and left subclavian arteries.³⁴ The systolic blood pressure in both upper extremities was 40 to 50 mm. Hg, and the diastolic pressure could not be measured. As would be anticipated, the oscilometric readings, which depend upon the pulsatile change in the caliber of the large blood vessels, were reduced to 0.4 and 0.7 unit. Nevertheless, the blood flow to the hand and forearm at a bath temperature of 32° C. was normal; the readings were 12.0 c.c. and 1.1 c.c. per minute per 100 c.c. of limb volume, respectively. The skin temperature readings for the upper extremity were also within normal limits.

It would seem, then, that skin temperature measurements give little or no indication of changes in the circulation through the muscles. Further, the rather prevalent practice of using the finger tips and toes for investigating general responses in skin circulation is open to criticism because of the presence in these two areas of specialized blood vessels—the arteriovenous shunts. In respect to the oscilometer, the readings

are probably not modified significantly by blood flow through small collateral vessels, which, as Scott and Morton³⁵ have shown, play an important role in maintaining blood supply to the distal parts of a diseased limb. In view of these objections, it can be concluded that neither of these methods necessarily reflects total blood flow changes in an extremity.

At this point it must be stressed that all of the results herein reported were obtained following a *single* administration of the various drugs. We are well aware that many authors, using some of the procedures previously mentioned, have reported alleviation of symptoms only after a series of treatments. Hence, the fact that we did not observe an increase in peripheral blood flow with our method of study does not necessarily contradict their results. For, if a drug or a procedure is considered to have a beneficial effect because, in some as yet unexplained manner, it tends to increase collateral circulation after repeated trials, or because it stretches the venocapillary bed, as de Takats, et al.,³⁶ suggest is the reason for using intermittent venous occlusion, our observations cannot be utilized in its evaluation. On the other hand, if the drug or procedure is advocated for its immediate *vasodilating* action, it would be expected that this effect should be demonstrable even with a single administration.

SUMMARY AND CONCLUSIONS

By means of the venous occlusion plethysmographic method, the vasodilating action of a number of procedures used in the treatment of peripheral vascular disease was studied on a series of patients with peripheral circulatory impairment, on a series of patients with various mental states, and on a group of normal subjects.

It was found that, with a single administration, calcium gluconate, "Padutin," papaverin, "Spasmalgin," and thiamin chloride produced only a slight increase, or none at all, in the blood flow to the hand, forearm, leg, and foot. Alcohol, stilbestrol, and histamine generally increased the blood flow to the hand, but not to any other portions of the extremities. Hypertonic saline solution produced an augmentation of the flow to the hand, leg, and foot in only one-third of the trials. The intermittent application of a venous occlusion pressure for a period of two to three hours did not result in the production of a significant increase in peripheral blood flow.

Evidence was presented to indicate that the commonly employed clinical methods, namely, the skin temperature thermometer and the oscillogram, do not necessarily reflect or parallel changes in total blood flow to an extremity.

The authors wish to express their appreciation to Dr. S. Silbert and Dr. E. A. Baber for their help in supplying the patients used in this study, and to Dr. K. H. Katzenstein and Mrs. Robert Senior for their cooperation in carrying out the experiments.

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DISCUSSION

DR. BENJAMIN JABLONS, New York.—I believe that studies which are made with the plethysmograph should be accepted with a certain degree of reserve. We have made similar studies in evaluating therapeutic procedures in peripheral vascular disease, using methods which Dr. Abramson criticized, namely, surface and subcutaneous temperature measurements and oscillometry. We have come to some conclusions which are not entirely in agreement with those which Dr. Abramson has reported this morning.

For instance, we have studied the effect of nicotinic acid on some of our patients, and have found, in agreement with his report, that there is very little change in the surface temperature. There is, however, a marked drop in the muscle temperature. Also, there is a slight to moderate degree of diminution in the amplitude of the peripheral arterial pulsations, as determined by oscillometric recordings. Under the capillary microscope we have found that there is a narrowing of the arteriolar limb of the capillary, with a tendency to stasis in the venous limb of the capillary. Now, it must naturally be assumed that if there is stasis in the venous system as a result of the diminished *vis a tergo*, then the volume of the limb will naturally be increased. If, therefore, one takes the plethysmographic record as an index of blood flow, one is likely to assume erroneously that there is an increased flow of blood through the limb, when what occurs is merely an increased amount of fluid stagnant in that limb.

We, therefore, believe that the use of the oscillometer, which will indicate fluctuations in the amplitude of the arterial pulse, and surface temperature measurements, which indicate, of course, increased circulation through the capillaries, are much more likely to give the information that is valuable in determining the merit of various therapeutic procedures. I am in thorough agreement with Dr. Allen in regard to the value of surface temperature increases as an index of improvement in circulation when it is needed.

DR. NATHAN D. WILENSKY, Brooklyn, N. Y.—It is very obvious that the disagreement between the conclusions of Dr. Linton, which have just been presented, and those of Dr. Abramson on the effect of intermittent venous occlusion on arterial flow requires careful study in order to be comprehensible. Such divergent conclusions make it necessary to ascertain, first, whether the method employed for investigating the rate of arterial flow is reliable.

Several months ago Dr. Abramson published a paper in the *AMERICAN HEART JOURNAL* in which he demonstrated a large number of artifacts which appear in the tracings and create a situation which frequently may be interpreted as part of the physiologic phenomena, but, in reality, represents errors in plethysmographic technique.

In spite of the fact that this paper was devoted to the subject of artifacts, Dr. Abramson used certain criteria to interpret the effect of venous occlusion on the rate of arterial flow, and became an easy victim of artifacts which he used for physiologic interpretations.

In our own plethysmographic studies we found that the drop of the needle which follows immediately upon the release of the venous pressure is not the result of a decline in the volume of the limb below the control level, but is an artifact which we could produce at will.

This peculiar deviation from the observed plethysmographic studies of Lewis and Grant can easily be produced by applying the cuff in such a manner that the skin is pulled out of the boot. With proper support by means of sandbags, and by maintaining the knee flexed at an angle of 30°, this artifact can be avoided. Further evidence that this observation is a result of an error in technique can be found in Abramson's own studies, in which he demonstrated this phenomenon only in the lower extremity, but could not produce it in the upper extremity. I fail to understand this difference in observations, except in so far as it indicates that the technique in the lower extremity is more susceptible to error. In view of the fact that Abramson's studies produce different curves in the upper and lower extremities, one must be very careful about interpreting plethysmographic records in studying the constitutional effects of therapeutic agents on arterial flow.

It certainly appears that the thermostromuhr method which Linton employed is a much more accurate method for measuring absolute rate of flow through major vessels.

DR. DAVID I. ABRAMSON, Cincinnati, Ohio.—In reference to Dr. Jablons' statement, we are not interested in measuring the volume of an extremity, for this procedure does not necessarily give any information concerning peripheral blood flow. An increase in volume may be caused by a number of different factors, as, for example, a passive or active dilatation of veins, as well as dilatation of arteries.

The method of venous occlusion, as used in measuring blood flow, consists of applying a pressure to the proximal portion of the extremity which is sufficiently high to prevent the flow of blood out of an extremity—at least for the first few seconds—but not high enough to interfere with inflow of blood. As a result, there is an increase in the volume of the extremity; the rate of swelling is dependent upon the rate at which the blood flows in. This increase in volume is recorded on a drum, and the quantity of blood entering the extremity in the first second following the application of the pressure is ascertained. From this one can calculate a figure which probably represents unopposed blood flow to the limb.

The above statements also apply to Dr. Wilensky's criticism. The drop in base line to which he refers is not an artifact. In any event it has obviously nothing to do with the method of blood flow measurement which was used in this study as more careful perusal of the papers in question will show.

VENOUS STASIS IN THE CORONARY CIRCULATION

AN EXPERIMENTAL STUDY

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THE purpose of this article is to record data concerning stasis in the venous circulation of the heart. Any addition to the methods of treating coronary artery disease should be investigated. The available medical methods by drugs and rest are indirect. Perhaps a direct operative method can be evolved which will improve the vascular bed in the heart.

Ligation of a major vein and a major artery elsewhere in the circulatory tree has received considerable study. Both clinical and experimental observations support the conclusion that after a major artery to an extremity has been ligated the incidence of ischemic necrosis in the extremity is reduced by ligation also of the major vein. Surgeons accept this as a principle in surgery. According to Halsted, the idea originated with the Russian surgeon Von Oppel,¹ in 1908. On the basis of clinical observations Sir George Makins^{3, 4} became an advocate of vein ligation with the artery. There are now considerable experimental data on this subject. Some of the experimental data are conflicting. In general, however, it appears that the incidence of necrosis is reduced by ligation of the vein with the artery. A brief résumé of this experimental work is given.

Brooks and Martin,⁵ 1923, ligated the femoral artery in rabbits and found that the pressure distal to the ligation fell markedly in the arterial system and slightly in the venous system. When ligation of the femoral vein was added to this experiment, the venous pressure rose markedly and the arterial pressure also became higher. They found that 72.5 per cent of 21 animals developed necrosis of the leg after ligation of the artery and 33.3 per cent of 18 animals developed necrosis after ligation of both artery and vein. The conclusions by these experimenters were that simultaneous ligation of vein and artery (1) increased intravascular pressure in both arteries and veins, (2) decreased the volume flow of blood and (3) decreased the incidence of necrosis. It would appear, therefore, that a beneficial effect can be produced in the presence of a reduction in blood flow. Holman and Edwards,⁶ 1927, found that the retrograde flow from the arterial stump distal to the ligation was increased by ligation of the vein. These experimenters concluded that ligation of the vein actually increased the flow distal to the arterial ligation. Brooks and Martin noted a reduction in temperature of the leg after ligation of the femoral artery and a further reduction in temperature when ligation of the vein was added to ligation of the artery. On this basis they concluded that blood flow was reduced by arterial ligation and still further reduced when ligation of vein was added to ligation of artery.

Theis,⁷ 1928, made observations on the amount of blood flowing from the peripheral end of the ligated and divided femoral artery. He found that the retro-

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Aided by a grant from the Josiah Macy, Jr. Foundation.

Received for publication July 29, 1940.

grade flow with artery alone ligated was less immediately than the retrograde flow with artery and vein ligated. The retrograde flow within an hour was the same in each type of experiment and three weeks later was greater in the arterial ligation than in ligation of both vein and artery. He assumed that the difference was explained by a better collateral circulation after ligation of the artery alone. However, this work is open to the criticism raised by Brooks that the flow of blood from the distal end of the divided artery did not represent the actual minute volume flow through the periphery of the limb. Furthermore, Theis found that the vascular bed, as determined by the roentgen appearance of the injected limbs, was greater immediately after ligation of the artery and vein; but that three weeks after ligation of the vessels, the vascular bed was more richly developed when the artery alone was ligated. This latter finding is in contradiction to that noted by Pearse,⁸ 1927, that the vascular bed in the limb having the artery and vein ligated was much more abundant than that with the artery alone ligated, with the maximum degree of difference at the end of two weeks. Commenting on these observations, Brooks⁹ stated that the size of the blood vessels as determined by injection was not a reliable index of the actual volume flow through the tissues and that the condition of the vascular tree three weeks after a sudden arterial occlusion was not necessarily important in the study of the cause of gangrene. He claimed that venous ligation was only of temporary benefit. Mulvihill, Harvey, and Doroszka,¹⁰ 1931, in experiments on 7 dogs ligated the external iliac artery and vein in one extremity and the artery alone in the other extremity. Gangrene did not develop in either extremity. The temperature curves were identical on both sides. They found that the temperature dropped gradually to room temperature in each leg over a period of three hours. The temperature remained at that point for about three hours. Then it suddenly rose to normal body temperature where it remained. The greater part of this sudden rise in temperature took place in a period of twenty minutes. Mulvihill and his co-workers believed that this sudden rise signified the establishment of collateral circulation by means of a vasomotor mechanism. They concluded that simultaneous ligation of the vein had no demonstrable effect in aiding or retarding the development of collateral circulation. Montgomery,¹¹ 1932, noted that following ligation of the femoral artery the peripheral arterial and venous pressures rose when the vein was ligated, whether the latter was the superficial femoral, the iliac, the common iliac or the inferior vena cava. In general, the peripheral pressures became higher as the ligature was placed nearer to the heart. However, the volume flow was progressively decreased by placing the ligature nearer to the heart. Montgomery agreed with Brooks that the beneficial effects of venous ligation were not due to an increase in blood flow, but that the ligation of the vein re-established the reduced peripheral blood pressures to a level above the minimum necessary to maintain a sufficient distribution of blood throughout the venous capillary bed and preserved the head of pressure required for the passage of nutrient elements from the capillaries into the surrounding tissues.

Brooks, Johnson and Kirtley,¹² 1934, found that ligation of the artery alone in one hundred rabbits produced necrosis on gross examination in 46 per cent and that ligation of the artery and vein in 100 rabbits was followed by gross necrosis in only 4 per cent. Massive gangrene occurred in 29 per cent after ligation of the artery alone and in only 2 per cent after occlusion of both artery and vein. Late ulceration was present in about equal frequency in each group of animals. It would appear that the beneficial effects of venous ligation did not persist indefinitely but disappeared after a period of time. Brooks observed the contracture of soft tissues that developed after ligation of artery alone and after ligation of artery and vein. He found that the contracture of the tissues developed somewhat later and the inflammatory reaction in the tissues was less severe after arterial

ligation than after arterial and venous ligation. Contractures developed in 15 animals in which the arteries alone were ligated and in only 4 animals in which both arteries and veins were ligated. The difference between the two groups was more striking if the mortality rate was considered: 58 per cent of the animals lived five days or more with the artery alone ligated, while 70 per cent of the animals lived five days or more with the artery and vein ligated. Brooks and his co-workers stated that gangrene and necrosis were the immediate and direct effects of deficient blood flow; that contractures were the result of the process of repair and were evidence of a previous impairment of circulation sufficiently great to produce necrosis of vulnerable tissue. The decreased incidence of contractures after vein ligation demonstrated the preservation of vitality of the more vulnerable tissue during critical periods before the reestablishment of circulation through the collateral vessels.

Similar studies on the veins and arteries of the hearts of dogs were carried out by Gross, Blum, and Silverman.¹³ With complete occlusion by ligation or other methods (escharotics, etc.) of the coronary sinus where it entered the right atrium, they obtained a mortality rate of 42 per cent (37 out of 89 dogs), occurring in the first twenty-four hours after ligation. Partial occlusion of the coronary sinus, however, carried a mortality rate of 10 per cent (4 out of 39 dogs). Unsuccessful occlusion of the coronary sinus produced a mortality rate of 21 per cent (6 out of 29 dogs). As a control series, ligation of the descending ramus of the left coronary artery, performed at a point 2 cm. from the ostium of the circumflex artery, resulted in a mortality rate of 53 per cent (28 out of 53 dogs), occurring within twenty-four hours after ligation. Of the 25 dogs that survived all showed infarcts of the heart, and in 24 of these the infarcts were invariably of uniform size and large filling defects of the coronary tree were noted on injection with barium gelatin. Ligation of the descending ramus at the same location, one to eight weeks (average four weeks) after complete occlusion of the coronary sinus yielded a mortality rate of 55 per cent (16 out of 29 dogs) or the same as the mortality rate among the animals of the controls. Of the 13 dogs surviving the above procedure, 7 showed no infarcts and in the other 6 dogs all the infarcts were considerably smaller than the infarcts found in the controls. In these hearts in which both artery and vein were ligated, the vascular tree was increased in extent and the filling defects on injection were either absent or small. Ligation of the descending ramus one to six weeks after partial occlusion of the coronary sinus resulted in a mortality rate of 31 per cent (9 out of 29 dogs). Of the 20 dogs surviving in the above experiments, 2 of the hearts showed no infarcts, 9 had infarcts much smaller than those of the controls, and 9 had infarcts of the same size as the hearts of the controls.

Gross and his co-workers claimed that coronary sinus occlusion produced an extensive and abundant dilatation of the intramyocardial collateral channels and the success of the procedure, discounting the mortality rate, depended upon the completeness of the coronary sinus occlusion. However, sudden and complete occlusion of the coronary sinus by itself was associated with a high operative mortality (42 per cent) and complete occlusion of the sinus did not change the mortality rate after ligation of the artery. Partial occlusion of the sinus by itself had a lower operative mortality and also lowered the mortality rate when ligation of the descending coronary artery was done subsequently. The infarcts obtained in the dogs with partial occlusion of the sinus were smaller than those obtained without any obstruction of the sinus but they were not as small as those obtained after complete obstruction of the sinus. Gross and his coworkers concluded that "complete or even partial occlusion of the coronary sinus, whether this be permanent or transient, affords a definite method of anatomically and functionally enriching the coronary bed to such an extent that infarction may be either completely prevented

or minimized." Thus, they base their enthusiastic conclusions of the beneficial effects of sinus ligation on the presence and size of infarcts, stating that the mortality rate was unaffected except in partial sinus occlusion.

Katz, Jochim, and Bohning¹⁴ found that occlusion of the coronary sinus resulted in a decrease in the total coronary artery inflow. These authors concluded that there was no rationale to ligation of the coronary sinus as a method to increase the coronary arterial bed.

Gregg and Dewald^{16,17} carried out physiologic studies after ligation of coronary vessels. They found that the pressure in the coronary sinus rose to the level of aortic pressure after the sinus was ligated. They found the contour and time relations of the venous pressure curves to resemble closely the curves obtained from the coronary artery. They also found that the pressure in the peripheral coronary arterial bed was increased by ligation of the coronary sinus. The inflow into the left coronary artery was significantly reduced by sinus ligation. They ligated the left descending coronary artery and coronary sinus and found that the systolic pressure in the artery peripheral to the ligature was approximately equal to or even higher than the aortic systolic pressure. They stated that this pressure had its source largely in other nonoccluded arteries. Also, the more proximal the ligation of the vein to the sinus, the higher was the peripheral coronary pressure. The retrograde blood flow from the left descending coronary artery was markedly elevated after the coronary sinus was ligated. When the artery was ligated and cut, the retrograde flow was about 1 c.c. per minute. After ligation of the coronary sinus the retrograde flow from the artery was as high as 39 c.c. per minute; the maximum peripheral flow was reached in from ten to thirty minutes and did not immediately return to control backflow figures following release of the ligature around the sinus. This value of 39 c.c. per minute approaches or equals the volume of blood which might be expected to flow into the central nonoccluded coronary artery. The retrograde blood was highly unsaturated, containing only 3 to 4 volumes per cent oxygen. The oxygen content of blood drawn from the coronary sinus under normal conditions was 8 volumes per cent. They found that the myocardium failed to contract over the area supplied by the ligated artery. They also found that occlusion of the sinus had practically no effect on the circulation in the right side of the heart. Gregg and Dewald do not believe that venous ligation is a method of "choice" for encouraging the blood supply to a potentially infarcted area of the myocardium.

Thornton and Gregg¹⁸ studied the problem after the coronary sinus had been occluded thirty days. They found that the measurements obtained by Gregg and Dewald had practically returned to normal levels. It would appear, then, that the alterations in the circulation produced by occlusion of the coronary sinus were transient in their duration. Gregg, Thornton, and Mautz¹⁹ studied the magnitude, adequacy and source of collateral blood flow and pressure in chronically occluded coronary arteries. It was found that after permanent occlusion of any of the major coronary branches, there was a marked increase in the peripheral coronary pressure values, even approaching the aortic systolic pressure; the peripheral coronary pressure curves were altered and some showed patterns scarcely distinguishable from the aortic pressure curves. Also, the retrograde blood coming from the peripheral end of the occluded coronary artery was 30 to 40 c.c. per minute. On the basis of these observations the authors concluded that a considerable collateral circulation develops following chronic occlusion of the coronary arteries. Furthermore, the retrograde blood could not be differentiated from arterial blood on the basis of its oxygen and carbon dioxide content. They further stated that such volume flows of retrograde blood were sufficient for the metabolic needs of the potentially infarcted myocardium, since the myocardial region exhibited normal contractions except in areas of scarring.

Fauteux,²⁰ of Montreal, ligated the magna cordis vein and the descending ramus of the left coronary artery. He concluded from his experiments that ligation of this vein reduced the mortality that follows ligation of the artery alone. Fauteux was eager to ligate this vein in patients with sclerosis of the descending ramus of the left coronary artery and recently carried out this operation.

ADDITIONAL EXPERIMENTS ON LIGATION OF CORONARY ARTERY AND VEIN

We carried out experiments on this subject for the purpose of obtaining the answer to two questions: (1) whether ligation of coronary veins reduced the mortality after ligation of an artery and (2) whether ligation of veins brought about a reduction in the size of the infarct. The artery selected for our study was the descending ramus of the left coronary artery just below the bifurcation of this artery (Fig. 1). The veins ligated were either the coronary sinus where it entered the right atrium (Fig. 2) or the magna cordis vein where it lay beneath the left auricle (Fig. 3). In some of the experiments the veins from the right ventricle were ligated as they entered the right atrium, thus producing stasis in almost the entire venous system of the ventricles.

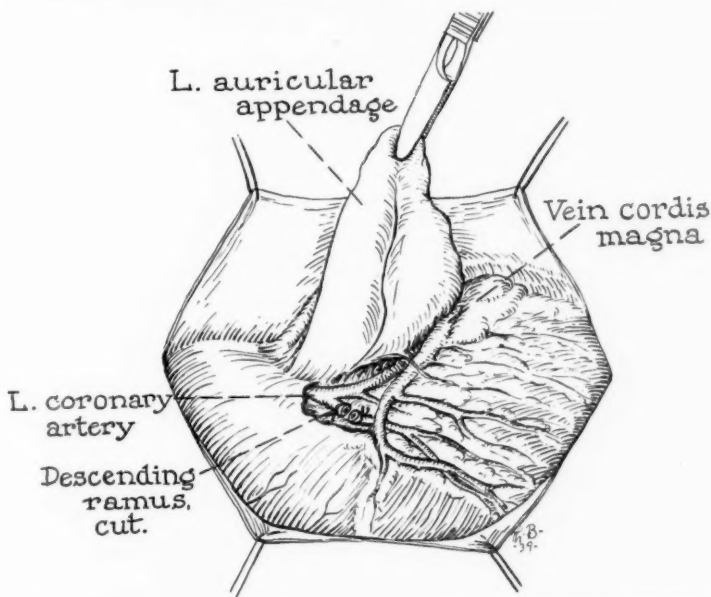


Fig. 1.—The left coronary artery was exposed at its bifurcation into the ramus descendens and the ramus circumflexus. The ramus descendens was isolated, doubly ligated, and cut between ligatures. The level for ligation was always here, never at a variable point along the artery.

Ligation of Coronary Veins.—Ligation of the coronary veins is followed by slowing of the heart rate, cyanosis of the ventricles, distention of veins, and enlargement of the heart. These observations were also made by Gross and his co-workers. The mortality rate following complete ligation of the coronary sinus in our hands was about 2 per cent. Gross, Blum, and Silverman reported a mortality of 42 per cent follow-

ing ligation of the coronary sinus. This great difference in mortality can be accounted for only on the basis of surgical technique, mechanical respiration, anesthesia, and avoidable complications to operation.

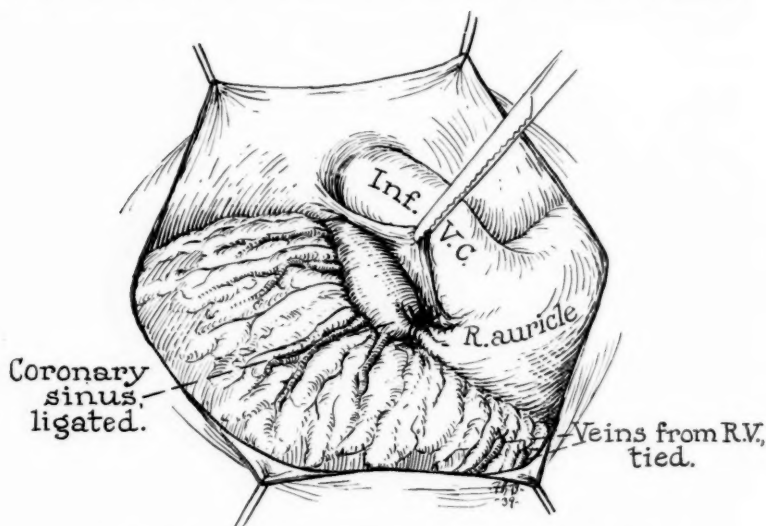


Fig. 2.—The coronary sinus was dissected and ligated with silk.

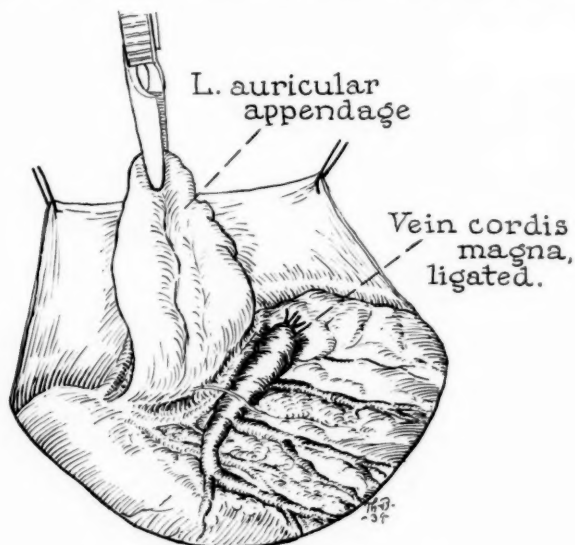


Fig. 3.—Ligation of magna cordis vein.

Ligation of Coronary Artery.—The left coronary artery was dissected at its bifurcation. The descending ramus was doubly ligated and cut immediately below its bifurcation. Every care was taken to avoid all factors that might increase the mortality rate. Three series of 10 dogs each were done at widely spaced intervals of time. The mortality

was 9, 8, and 7, or a total of 24 in 30, a mortality rate of 80 per cent (Table I). Seven or 29 per cent died within five to thirty minutes after

TABLE I
LIGATION OF DESCENDING RAMUS OF LEFT CORONARY ARTERY

NUMBER OF DOGS	DIED	SURVIVED	MORTALITY RATE
10	9	1	90%
10	8	2	80%
10	7	3	70%
Total 30	24	6	80%

ligation; 15 or 63 per cent died within two to eighteen hours; one died fifteen days, and another eighteen days, after ligation. Complete autopsy failed to reveal any other cause of death in these last two dogs so that the cause of death must be ascribed to the ligation of the artery. These two dogs had infarcts which were among the smallest that were observed in the series of control experiments. Nothing that could be considered as infarcts was present in the dogs that died within eighteen hours except for questionable color changes of the myocardium. These color changes on microscopic examination failed to reveal any variation from the normal appearance of heart muscle. The six dogs that recovered were observed over a period of twelve days to eight months; the dog living twelve days was killed because of severe distemper; the remainder were killed from five weeks to eight months after ligation of the artery.

Ligation of Coronary Vein and Artery.—The first series consisted of 10 dogs. The artery was dissected. The magna cordis vein was ligated. Within a few minutes after ligation of this vein the artery was ligated and cut. Three of these dogs lived and 7 died (5 of which died from five to thirty minutes after ligation); mortality rate 70 per cent. The second series consisted of 10 dogs. In this series the coronary sinus was ligated and after an interval of three to six days (average 3.8 days) a second operation was done and the artery was ligated and cut. Two of these dogs lived and 8 died (five of which died from five to thirty minutes after ligation); mortality 80 per cent. The third series consisted of 10 dogs. In this series the coronary sinus was ligated and after an interval of seven to seventeen days (average thirteen days) a second operation was done and the artery was ligated and cut. Five of these dogs lived and 5 died (2 of which died from five to thirty minutes after ligation, 1 about eighteen hours later, 1 about thirty-six hours later, 1 about five days later); mortality 50 per cent. The fourth series consisted of 10 dogs. In this series the magna cordis vein was ligated and after an interval of six weeks a second operation was done and the artery was ligated and cut. Five of these dogs lived and 5 died (4 of which died five to thirty minutes after ligation); mortality 50 per cent. The fifth series consisted of 17 dogs. In this series the coronary sinus was ligated and after an interval of four months a second operation was done and the

artery was ligated and cut. Seven of these dogs lived and 10 died (5 of which died five to thirty minutes after ligation, 4 at the end of eighteen hours and 1 in twenty-nine hours); mortality 59 per cent (Table II).

TABLE II

LIGATION OF VEIN AND LIGATION OF DESCENDING RAMUS OF LEFT CORONARY ARTERY

SERIES	NUMBER OF DOGS	VEIN LIGATED	INTERVAL BETWEEN LIGATION OF VEIN AND LIGATION OF ARTERY	DIED	SURVIVED	MORTALITY RATE
I	10	Magna Cordis	At same operation	7	2 killed, 10 months 1 killed, 8 days, distemper	70%
II	10	Coronary Sinus	3 to 6 days Average 3.8 days	8	2 killed, 2 months	80%
III	10	Coronary Sinus	7 to 17 days Average 13 days	5	2 killed, 4 weeks 2 killed, 3 weeks 1 killed, 2 weeks	50%
IV	10	Magna Cordis	6 weeks	5	4 killed, 8 months 1 killed, 3 months	50%
V	17	Coronary Sinus	4 months	10	7 killed, 3 months	59%
Total	57			35	22	61%

It was found that many animals died from ventricular fibrillation five to thirty minutes after ligation of the artery. If the animal survived this early period it usually lived several hours and was found dead in the cage the next morning. The deaths can be grouped as immediate and delayed. In the control group death was immediate, i.e., within thirty minutes, in 29 per cent and delayed in 71 per cent. In the entire group in which vein and artery were ligated, death was immediate in 60 per cent and delayed in 40 per cent.

At the time of re-operation for ligation of the artery, the heart itself presented a variable picture. The degree of venous engorgement varied widely in the same series. Three to six days after occlusion of the coronary sinus, the heart was usually enlarged due to venous engorgement and the contractions were somewhat sluggish. The veins, even minute ones, were distended. They were easily torn and bled freely. In some experiments hemostasis was difficult to obtain because of the elevated venous pressure. Two weeks after venous ligation the engorgement of veins and the distention of the heart were less marked and the heartbeat appeared to be stronger. Six weeks after ligation of the magna cordis vein the distention of the veins was still observed but it was slight. At four months distention of veins was not observed. We found definite evidence of fibrosis in the fat around the coronary artery. This was observed in our dissection of the artery and was found in practically all hearts in which venous stasis had been produced. It can be mentioned

here that Brooks and his co-workers noted fibrosis in their experiments on the extremities. However, the fibrosis was not found in the heart muscle either grossly or microscopically.

Analysis of Infarcts.—Difficulty was encountered in making measurements of the infarcts. The infarct could not be measured before degenerative changes had sufficient time to take place. An infarct of less than twenty-four hours' duration showed only macroscopic color change in the myocardium. Under the microscope the heart muscle appeared normal, as a rule, up to twenty or twenty-four hours. Necrosis, separation of muscle bundles, and poor staining affinity then appeared. Later on the infarct became a cicatrix. The extent of the cicatrix was variable. In some specimens the septum was slightly involved; in others the cicatrix extended across the entire septum. The thickness of the cicatrix was variable. In some specimens it extended across the entire thickness of the ventricular wall; in other specimens it involved only part of the wall.

We observed these infarcts as closely as we could and we can say that the cicatrices obtained in the control experiments were about the same size as those obtained in experiments after vein and artery ligation. The specimens in the third series of vein and artery ligation with an interval of seven to seventeen days and with a 50 per cent mortality showed infarcts that were slightly smaller than the infarcts of the controls. In the other series the difference, if any, was so slight that we could not recognize it.

It was thought that injection of the coronary arteries with barium gelatin might be of some value in determining the size of the intercoronary communications. The technique of the injection was identical in all hearts and one technician injected all specimens. The circumflex branch of the left coronary artery and the right coronary artery were injected. The injection mass that entered the descending ramus of the left coronary artery did so by way of intercoronary communications with the two injected arteries. It was seen that there was good filling of the distal portions of the left descending coronary artery in every heart that survived ligation of the artery, whether the vein was or was not ligated also. This occurred because communications with the right and with the left circumflex arteries developed. This development of intercoronary communications is an important compensation for coronary artery obstruction in the dog. In these hearts that survived arterial ligation, most of the infarcts showed a moderate number of injected arteries even in areas of marked scarring. In an analysis of 22 hearts in which the artery only was ligated, 50 per cent had good filling of the descending ramus, 10 per cent had poor filling and 40 per cent had no filling of the artery. In an analysis of 54 specimens in which vein and artery were ligated, 76 per cent showed good filling, 13 per cent had

poor filling and 11 per cent showed no filling of the distal end of the descending ramus of the left coronary artery. It appears then that venous ligation has a tendency to open intercoronary communications. However, this was not sufficient to prevent the development of an infarct in a single experiment.

Partial Occlusion of Coronary Artery.—We carried out experiments in which the descending ramus of the left coronary artery was partially and not completely occluded. The purpose was to increase the survival rate so that a larger number of specimens were available for study. We recognize that this procedure adds a variable factor to the experiment. Eleven pairs of dogs were selected. Each pair was about the same size and weight. The descending ramus was dissected at the bifurcation of the left coronary artery as in the other experiments. In one of each pair the magna cordis vein was ligated well around the left posterior aspect of the heart about 3 cm. from the coronary sinus. To do this the heart was rotated. After this ligation was made, a ligature was placed around the artery and tied to include with the artery a metal stilette about one millimeter in diameter. The stilette was then removed. However, it was quite impossible to produce the same degree of occlusion in each pair of dogs. When the hearts were examined we found that our tendency had been to give a greater degree of occlusion to the experiment involving both vein and artery, as compared to the experiment with artery alone. The results are given in Tables III and IV. These dogs were killed three months after operation.

TABLE III
PARTIAL OCCLUSION OF DESCENDING RAMUS OF LEFT CORONARY ARTERY

EXPERIMENT	LIVED	DIED	MYOCARDIUM	APPROXIMATE DEGREE OF ARTERIAL OCCLUSION
1	+		No infarct	90%
2	+		Large infarct	100%
3	+		Small infarct	75%
4	+		No infarct	75%
5		12 hours	Too early to show infarct	75%
6	+		No infarct	95%
7		12 hours	Too early to show infarct	95%
8		14 days	No infarct	80%
9	+		No infarct	85%
10	+		Infarct of medium size	90%
11		3 hours	Too early to show infarct	90%

In the control group with ligation of artery alone 4 died and 7 recovered. The mortality rate with the artery alone was 36 per cent and the degree of occlusion as estimated by observation was 86 per cent. One specimen in this group showed complete occlusion. The mortality rate with vein and artery ligated was 18 per cent and the degree of occlusion as estimated by observation was 95 per cent. Five specimens in this group showed complete occlusion. Halsted in his work on blood vessel

TABLE IV

LIGATION OF MAGNA CORDIS VEIN AND PARTIAL OCCLUSION OF DESCENDING RAMUS OF LEFT CORONARY ARTERY

EXPERIMENT	LIVED	DIED	MYOCARDIUM	APPROXIMATE DEGREE OF ARTERIAL OCCLUSION
1	+	12 hours	Focal areas of fibrosis only	100%
2	+		No infaret	95%
3	+		Too early to show infaret	100%
4	+		No infaret	90%
5	+		Small infaret with focal areas of fibrosis	100%
6	+	12 hours	No infaret	95%
7	+		No infaret	90%
8	+		Too early to show infaret	100%
9	+		No infaret	80%
10	+		Medium size infaret	100%
11	+		Medium size infaret	95%

surgery showed that a ligature that almost completely occluded an artery when it was applied could become completely occlusive after a cicatrix formed around the ligature. It is our opinion that this occurred in these experiments. Three specimens with complete occlusion of the artery and vein showed infarcts that were smaller than any infaret produced by complete arterial occlusion either in this series or in the other series of 36 control experiments. The specimens with vein ligation plus partial arterial ligation showed less destruction of the myocardium than did the specimens with partial arterial ligation alone.

DISCUSSION AND CONCLUSIONS

Does ligation of the vein reduce the mortality rate following ligation of a coronary artery? The answer to this question was difficult to ascertain and we had to carry out many experiments to obtain sufficient data. We had to use 30 dogs to get a standard for comparison. A considerable variation existed in the mortality of this group. The total mortality for complete occlusion of the artery was 80 per cent, 24 out of 30. Likewise, a considerable variation existed in the mortality following occlusions of vein and artery. The total mortality was 61 per cent, 35 out of 57. A glance at the experiments in the latter group shows that the mortality was not reduced in the series in which ligation of the vein was followed by ligation of the artery at the same operation or after an interval of three to six days. Perhaps the two operations in succession should be given some consideration in the mortality but this we cannot evaluate. The figures indicate that the mortality is reduced if a period of seven days to four months intervenes between ligation of vein and ligation of artery. In these groups the mortality was 50 per cent, whereas, the lowest mortality in any of the three control series of 10 each was 70 per cent.

More conclusive results were obtained in the experiments with partial ligation of the artery. In this group the mortality was lower and the degree of occlusion was greater than with venous ligation plus partial occlusion of the artery. A larger number of dogs survived a greater degree of arterial occlusion in the group in which ligation of the vein was added to the occlusion of the artery.

Does ligation of the vein reduce the size of the infarct? In the experiments in which the artery was completely occluded we could see no definite difference in the size of the infarct whether the vein was or was not occluded. A possible exception to this statement was in the third series in which the infarcts were slightly smaller than were those of the control group. In the experiments with partial ligation of the artery, the difference in the size of the infarcts was definite. In these experiments it appears that ligation of the vein does reduce the size of the infarct as compared to the infarct following partial occlusion of the artery only. The infarcts in this group of experiments with ligation of the vein plus partial occlusion of the artery were smaller than the infarcts with partial and less marked occlusion of the artery only.

Finally, we are confronted with the question of application of this work in the treatment of occlusion of the coronary arteries. Do the experiments show sufficient beneficial effect to indicate ligation of the coronary sinus or magna cordis vein in the human heart for the purpose of improving the coronary circulation in patients with coronary sclerosis? Our feeling about this is that the beneficial effect probably is not great enough to justify application. We would like to suggest that further measurements be made before considering this as a therapeutic procedure.

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THE SIGNIFICANCE OF DIAGNOSTIC TESTS IN THE STUDY OF PERIPHERAL VASCULAR DISEASE

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DURING the past few years numerous methods for estimating the degree and distribution of peripheral arterial occlusion and vasoconstriction have been described. These methods have added greatly to our clinical knowledge of vascular diseases such as arteriosclerosis obliterans, thromboangiitis obliterans, various vasospastic conditions, and numerous less common peripheral vascular disorders. They are aids in diagnosis and prognosis and help indicate appropriate therapy. In the past seven years 1,027 patients have been studied in the Peripheral Vascular Clinic of the Hospital of the University of Pennsylvania. Only 75 per cent of this number were found to have peripheral vascular disease (Table I). The present communication is presented in order to show the usefulness of diagnostic tests in evaluating the circulatory disorder from the standpoint of prognosis and treatment (Table II).

Frequently the tests served to confirm pathologic and functional diagnoses based on history and physical examination, usually they gave some additional information, and not uncommonly they changed the diagnosis. In a series of seventy-one consecutive cases of peripheral arteriosclerosis, thromboangiitis obliterans, or abnormal vasoconstriction (Table III), the diagnosis which was made from the history and physical examination was confirmed by diagnostic tests in 53 per cent, was amplified ("functional diagnosis") in 30 per cent, and was refuted in 17 per cent. Accuracy of prognosis was generally improved as a result of employing the diagnostic tests, although the remittent character of the disease in many cases determined the ultimate outcome.

Vasodilatation tests gave the most reliable information. Frequently they were used to substantiate the clinical impression formed from the history and physical examination, and in such instances they established the diagnosis more firmly on a physiologic basis. In those cases in which the tests were functionally diagnostic the immediate prognosis was established. In no case was misleading information gained from properly performed tests. A list of the tests is given in Table IV.

ELEVATION AND DEPENDENCE OF LIMBS

Several tests are a part of the routine examination of patients who are suspected of having peripheral arterial disease. The simplest of these is

From the Robinette Foundation, Medical Clinic of the Hospital, and The Harrison Department of Surgical Research, University of Pennsylvania.

Presented before the American Heart Association, June 8, 1940, New York, N. Y.

Received for publication Aug. 2, 1940.

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TABLE I
DIAGNOSES OF ALL PATIENTS SEEN IN THE PERIPHERAL VASCULAR CLINIC
1933-1940*

"STRICTLY" PERIPHERAL VASCULAR DISEASE DIAGNOSES	
1. Arteriosclerosis—without diabetes	252
2. Arteriosclerosis—with diabetes	94
3. Thromboangiitis obliterans	121
4. Abnormal vasoconstriction (a) Raynaud's disease	19
(b) other	
5. Varicose veins	36
6. Thrombophlebitis (a) acute	16
(b) chronic	7
7. Embolism	16
8. Acrocyanosis	13
9. Scleroderma	11
10. Lymphedema	9
11. Varicose ulcer	9
12. Erythromelalgia	5
13. Scalenus anticus syndrome	4
14. Congenital arteriovenous fistula	3
15. Cervical rib	2
16. Sensitivity to tobacco	2
17. Thrombosis saphenous vein	2
18. Recurrent lymphangitis (idiopathic)	2
19. Femoral artery thrombosis of unknown origin	2
20. Recurrent phlebitis of unknown origin	2
21. Traumatic aneurysm femoral artery	1
22. Traumatic arterial occlusion (by cast)	1
23. Traumatic arterial spasm	1
24. Thrombosis? of abdominal aorta	1
25. Axillary artery thrombosis, cause unknown	1
26. Traumatic vasospasm (pneumatic hammer)	1
27. Oil embolus (bismuth in oil)	1
28. Traumatic arteriovenous aneurysm	1
29. Thrombosis common iliac veins	1
30. Axillary vein thrombosis	1
	722
OTHER PERIPHERAL VASCULAR DISEASES	
1. Cerebral vascular, symptoms in extremities	10
2. Frostbite of digits	6
3. Hypothyroidism—coldness in extremities	3
4. Polycythemia vera—erythromelalgic symptoms	2
5. Localized scleroderma—morphoea	2
6. Poliomyelitis	1
7. Edema of unknown origin	1
8. Postoperative carcinoma of breast	1
9. Injury to lymphatics with obstruction	1
10. Stump edema—poor lymphatic return	1
11. Thrombosis of central retinal artery	1
12. Surgically induced hypotension	1
13. Arteriosclerosis of spinal cord	1
14. Arterial spasm secondary to coronary artery disease	1
15. Causalgia	1
	33

*Final diagnoses in 1,027 cases from the Peripheral Vascular Clinic of the Hospital of the University of Pennsylvania.

 ENTIRELY NONVASCULAR DIAGNOSES MADE IN THE PERIPHERAL
VASCULAR CLINIC

1. Hypertrophic arthritis		28
2. Pes Planus		16
3. Neurosis		13
4. Peripheral neuritis in diabetic patients		10
5. Peripheral neuritis in nondiabetic patients		10
6. Dermatophytosis (primary cause of symptoms)		9
7. Atrophic arthritis		6
8. Obesity		6
9. Menopausal paresthesias		6
10. Referred for studies of sympathetic system		6
11. Traumatic neuritis—cast, trauma		5
12. Sprained ankle		4
13. Sciatica		3
14. Low blood chlorides		3
15. Erysipeloid of leg—dermatophytosis?		3
16. Shortening of tendon Achilles		2
17. Temporary neuritis caused by salicylic acid		2
18. Syphilis		2
19. Meralgia paresthetica		2
20. Traumatic gangrene—nonvascular		2
21. Neurologic lesions		
chronic sclerosing myelitis	1	amyotrophic lateral sclerosis 1
posterolateral sclerosis	1	Charcot-Marie-Tooth disease 1
myelitis anesthesia	1	spastic paraplegia 1
Parkinsonism	1	progressive unilateral hemiatrophy 1
22. Intestinal malignancy		1
23. Gout		1
24. Hyperhidrosis		1
25. Infection of toe—nonvascular		1
26. Nonvascular ulcer on leg—traumatic		1
27. Fracture of metatarsals		1
28. Spondylolisthesis of lumbar vertebra		1
29. Neuritis of pregnancy		1
30. Club feet		1
31. Sprain fracture, external malleolus		1
32. Bursitis of popliteal space		1
33. Disuse atrophy		1
34. Nutritional edema		1
35. Pernicious anemia		1
36. Improper shoes		1
37. Herpes zoster		1
38. Hyperpituitarism		1
39. Congenital band around leg		1
40. Calcium deficiency		1
41. Old osteomyelitis		1
42. Bursitis (subacromial)		1
43. Myositis		1
		<hr/> 168
Diabetes without peripheral arterial disease		31
Diseases with symptoms in extremities not diagnosed in the Peripheral Vascular Clinic		73
Total number of patients examined		<hr/> 1027

observation of the effect of position on skin color. While the patient reclines, the legs are raised and the degree and rate of blanching of the feet are noted. Normally, blanching is incomplete and slow; but blanching is complete within several seconds when many arteries are occluded. The patient then sits up and places the feet on the floor. If the subject

TABLE II
STRUCTURAL AND FUNCTIONAL CLASSIFICATION OF PERIPHERAL ARTERIAL CONDITIONS IN RELATION TO PROGNOSIS AND PRINCIPLES OF TREATMENT

"DIAGNOSIS"	PULSE OR OSCILLA- TIONS	BLOOD FLOW	PROGNOSIS	PRINCIPLE OF TREATMENT
1. Normal	++	Max. range of blood flow, varying promptly and automatically depending upon the needs of the tissues	---	-----
2. Abnormal vasoconstriction or spasm	++ or +	Max. range of blood flow in response to strong stimuli, but flow fails to increase automatically in response to <i>some</i> of the needs	Good	Vasodilator
3. Occlusion <i>Severe</i> (a) Uncomp. for by collat.	0	Negligible range of blood flow (usually fixed, sl. vasodilatation)	Poor	Decrease tissue needs Give time for collat. Mechanical methods of incr. bl. flow
(b) Partly comp. for by collat.	0	Decreased range of blood flow	Fair	Same, less intense
(c) Fully comp. for by collat.	0	Normal range of blood flow	Fair	Protect from trauma
(a) Uncomp. for by collat.	0 to +	Decreased range of blood flow	Fair	Decrease tissue needs; give time for collateral
(b) Partly comp. for by collat.	0 to +	Decreased range of blood flow	Fair	Same, less intensive
(c) Fully comp. for by collat.	0 to +	Normal range of blood flow	Fair	Protect from trauma
4. Mixed abnormal vasoconstriction and partial occlusion (a) Ocd. uncomp. for by collat.	0 to +	Decreased range of blood flow	Fair	Vasodilator, decrease needs
(b) Ocd. partly comp. for by collat.	0 to +	Decreased range of blood flow	Fair	Same, less intense
(c) Ocd. fully comp. for by collat.	0 to +	Normal range of blood flow	Fair to good	Vasodilator

TABLE III
CLINICAL VALUE OF TESTS

SEX	AGE	PERIPH. ARTERIAL DIAG., PATH. AND FUNCTIONAL		VALUE OF TESTS	FOLLOW-UP
		FROM HIST. AND PHYS. EXAM.	FROM HIST., P. EX. AND TESTS		
<i>No Peripheral Vascular Disease</i>					
F	57	?Arterioscl.	No P.V. disease	Diagnostic	5 yr. No P.V.D.
F	46	No per. vas. disease	No P.V.D.	Confirmatory	2 yr. No P.V.D.
F	36	?Per. vas. disease	No P.V.D.	Diagnostic	2 yr. No P.V.D.
M	38	No per. vas. disease	No P.V.D.	Confirmatory	2 yr. No P.V.D.
M	55	Diabetes, ulcer, no P.V.D.	No P.V.D.	Confirmatory	2 yr. No P.V.D.
F	23	No per. vas. dis.	No P.V.D.	Confirmatory	2 yr. No P.V.D.
<i>Arteriosclerosis With Occlusion</i>					
M	63	Arterioscl. ? severity	Arterioscl. good collat.	Funct. diag.	5 yr. Asympt.
M	65	Abnormal vasoconst.	Arteriosc. good collat.	Diagnostic	2 yr. Arteriosc.
F	66	Arteriosc. moderate	Arteriosc. good collat.	Confirmatory	7 yr. moderate
M	68	Arterioscl. severe	Arteriosc. severe	Confirmatory	2 yr. Asympt.
M	54	Arteriosc., ? grade	Arteriosc. good collat.	Funct. diag.	3 yr. Asympt.
M	75	Arteriosc. mod. severe	Arteriosc. good collat.	Funct. diag.	3 yr. Asympt.
M	58	Arteriosc. severe	Arteriosc. good collat.	Funct. diag.	5 yr. Asympt.
M	53	Arteriosc. gangrene	Arteriosc. fair collat.	Funct. diag.	5 yr. Asympt.
M	57	Arteriosc. severe	Arteriosc. fair collat.	Funct. diag.	2 yr. Asympt.
F	70	Arteriosc. slight	Arteriosc. slight	Confirmatory	4 yr. Asympt.
M	56	Arteriosc. ? degree	Arteriosc. moderate	Funct. diag.	2 yr. Asympt.
M	70	?Arteriosclerosis	Arteriosc. severe	Diagnostic	2 yr. no change
M	80	Arteriosc. severe	Arteriosc. poor collat.	Confirmatory	3 yr. Asympt.
M	63	Arteriosc. moderate	Arteriosc. good collat.	Confirmatory	3 yr. Inter. Cla.
<i>Diabetic Arteriosclerosis With Occlusion</i>					
M	46	Arteriosc. severe	Arteriosc. severe	Confirmatory	8 yr. Asympt.
F	51	Arteriosc. severe	Arteriosc. good collat.	Funct. diag.	3 yr. Asympt.
M	82	Arteriosc. severe	Arteriosc. fair collat.	Funct. diag.	5 yr. Asympt.
F	56	Arteriosc. moderate	Arteriosc. poor collat.	Funct. diag.	5 yr. Asympt.
F	60	Arteriosc. severe	Arteriosc. fair collat.	Funct. diag.	5 yr. Asympt.
M	62	Arteriosc. moderate	Arteriosc. rather severe	Confirmatory	2 yr. Asympt.
F	46	Arteriosc. moderate	Arteriosc. good collat.	Confirmatory	2 yr. Improved
M	57	Arteriosc. severe	Arteriosc. severe	Confirmatory	2 yr. Improved
M	46	?Arteriosc.	Arteriosc. spastic element	Diagnostic	3 yr. Asympt.
M	56	Arteriosc. ? grade	Arteriosc. mod. collat.	Funct. diag.	4 yr. Improved
M	56	Arteriosc. severe	Arteriosc. fair collat.	Funct. diag.	5 yr. Asympt.
F	54	Arteriosc. severe	Arteriosc. severe	Confirmatory	2 yr. no change
M	58	Arteriosc. moderate	Arteriosc. moderate	Confirmatory	2 yr. no change
F	61	Arteriosc. severe	Arteriosc. good collat.	Funct. diag.	2 yr. Imp., Fail.
F	45	?Arteriosc.	Arteriosclerosis, mild	Diagnostic	3 yr. Improved
F	54	Arteriosc. moderate	Arteriosc. fair collat.	Confirmatory	2 yr. Improved

Thromboangiitis Obliterans

M	34	T.A.O. severe	T.A.O. good collat.	Funct. diag.	2 yr. no change
M	35	T.A.O. severe	T.A.O. slight collat.	Confirmatory	2 yr. healing
M	35	T.A.O. severe	T.A.O. good collat.	Funct. diag.	3 yr. healed
M	33	T.A.O. severe	T.A.O. some collat.	Confirmatory	2 yr. just healed
M	37	T.A.O. severe	T.A.O. negligible collat.	Confirmatory	6 yr. recur. ulc.
M	38	T.A.O. severe	T.A.O. slight collat.	Confirmatory	5 yr. recur.
M	41	T.A.O. severe	T.A.O. negligible collat.	Confirmatory	4 yr. Asympt.
M	40	T.A.O. ? grade	T.A.O. good collat.	Confirmatory	5 yr. Inter. Cla.
M	35	T.A.O. severe	T.A.O. severe	Confirmatory	3 yr. Inter. Cla.
M	51	T.A.O. severe	T.A.O. severe	Confirmatory	2 yr. Improved
M	46	T.A.O. moderate	T.A.O. severe	Funct. diag.	2 yr. healing
M	42	Abnormal vasoconstriction	T.A.O. poor collat.	Diagnostic	4 yr. worse
M	32	T.A.O. severe	T.A.O. fair collat.	Funct. diag.	3 yr. much impr.
M	43	‡Arterial occlusion	T.A.O. fair collat.	Diagnostic	3 yr. Asympt.
M	44	T.A.O. moderate	T.A.O. good collat.	Funct. diag.	5 yr. no change
M	28	T.A.O. severe	T.A.O. fair collat.	Funct. diag.	2 yr. Asympt.
M	56	T.A.O. severe	T.A.O. poor collat.	Confirmatory	2 yr. Inter. Cla.
M	49	T.A.O. severe	T.A.O. severe	Confirmatory	2 yr. Toes Amput.
M	41	T.A.O. mild	T.A.O. good collat.	Confirmatory	3 yr. Asympt.
M	45	T.A.O. fair collat.	T.A.O. poor collat.	Funct. diag.	4 yr. Recur. ulcer
M	28	T.A.O. severe	T.A.O. severe	Confirmatory	2 yr. Recur. ulc's
M	39	T.A.O. severe	T.A.O. some collat.	Confirmatory	2 yr. Recur. ulc's
M	30	T.A.O. severe	T.A.O. poor collat.	Confirmatory	3 yr. Recur. ulc's
M	31	T.A.O. severe	T.A.O. poor collat.	Confirmatory	5 yr. Amput. leg
M	48	T.A.O. severe	T.A.O. severe	Confirmatory	5 yr. worse
M	45	T.A.O. severe	T.A.O. severe	Confirmatory	2 yr. Amput. toes
M	49	T.A.O. severe	T.A.O. poor collat.	Confirmatory	3 yr. Amput. leg
M	59	T.A.O. and arterioscl.	T.A.O. etc. severe	Confirmatory	2 yr. Pregangr's
M	58	T.A.O. and arterioscl. mod.	T.A.O. etc. fair coll.	Confirmatory	6 yr. Improved
M	52	T.A.O. and diab. art. severe	T.A.O. etc. poor collat.	Confirmatory	4 yr. Amput. legs

Abnormal Vasoconstriction

M	57	Diabetic arterioscl.	Abnormal vasoconstr.	Diagnostic	3 yr. Asympt.
F	24	Diabetic arterioscl.	Abnormal vasoconstr.	Diagnostic	8 yr. Asympt.
F	36	‡Arteriosclerotic	Abnormal vasoconstr.	Diagnostic	3 yr. Abn. Vasocon.
F	34	Arterioscl. severe	Abn. vasocon., mild arterioscl.	Diagnostic	6 yr. Asympt.
M	49	Abnormal vasoconstr.	Abnormal vasoconstr.	Confirmatory	3 yr. no change

The relation of (a) the diagnosis based on history and physical examination to (b) the diagnosis based on these with the aid of tests.

is normal, unless there is considerable vasomotor tone, the feet become a full pink color, and the veins fill within ten seconds. Arterial occlusion causes a delay in flushing and in venous filling. With severe, uncompensated arterial occlusion the delay may be half a minute or more, and the foot will then become deep red ("rubor") or cyanotic. These tests estimate the status of the arterial circulation only roughly, but are useful because they are simple. Normal variations in vasomotor tone may alter the results. Hypertension may prevent blanching on elevation. Varicose veins rarely allow falsely rapid venous filling in dependent feet.

TABLE IV
TESTS OF PERIPHERAL ARTERIAL DISABILITY

(A) Tests which are part of the physical examination.	
	Observation of local tissue nutrition; color of skin and temperature of skin.
	Palpation of pulses.
	Rate of blanching on elevation.
	Rate of flushing and filling of veins on dependency.
	Blood pressure in different limbs at various levels.
	Reproducing spasm by immersion of extremity in cold water.
(B) Tests of Capacity of Blood Flow (Vascular Function Tests) in Skin. Vaso-dilatation Tests.	
	Reflex heat.
	Heating extremities not tested. ^{11, 12}
	Heating the body. ^{13, 14, 15, 16}
	Dianthermy as source of heat. ²²
	Artificial fever—Typhoid vaccine. ^{17, 18}
	Alcohol ingestion. ¹⁹
	General anesthesia. ²²
	Peripheral nerve block with novocaine. ^{20, 21, 22, 23}
	Posterior tibial nerve.
	Ulnar nerves.
	Other nerves.
	Spinal anesthesia. ^{22, 24, 25}
	Procaine injection into paravertebral sympathetic ganglion chain. ²⁰
	Intracutaneous histamine injection test. ^{29, 30}
	Intradermal saline wheal test. ³¹
	Reactive hyperemia tests. ³⁷
	Arteries of upper extremities.
	Arteries of lower extremities.
	Matas' test for collateral circulation. ³⁸
(C) Tests of Capacity for Blood Flow (Vascular Function Tests) in Muscle.	
	Walking distance. ⁴⁰
	Ergographic measurements of muscle fatigue. ^{41, 42}
(D) Tests of past damage to arteries.	
	Oscillometry. ^{26, 27}
	X-ray for calcification of vessels.
	Arteriography. ⁴³

EXPOSURE TO COLD

Patients who present a history of abnormal vasoconstriction which is not apparent at the time of examination are tested by exposure to cold air or by immersing the affected limb in cold water (15 degrees C. for ten minutes). When the vasoconstriction is confined to the upper extremities, evidence of the presence of a cervical rib and the scalenus anticus syndrome¹ is sought.

VASODILATATION TESTS

The outcome of physiologic studies on the peripheral circulation is largely influenced by variations in vasomotor tone, that is, the degree of peripheral vasodilatation or vasoconstriction which is present at the time the test is made, for most of the tests estimate the rate of blood flow, and the circulation decreases in proportion to the degree of vasomotor tone. Wide fluctuations in vasomotor tone occur in response to various factors. Vasodilatation occurs in the skin in response to infection, to local heating, to heat applied elsewhere to the body, to a rise in body temperature, and to meals. Blood may flow through exercising muscle as much as ten to twenty times as fast as through resting muscle,² and through warm skin as much as a hundred times as fast as through cool skin.³ Changes in environmental temperature alter vasomotor tone to such an extent that there may be an even faster blood flow in a warm extremity in which there is some occlusion of vessels than in a cool extremity with normal vessels. Consequently, in studying the peripheral circulation it is essential to estimate the degree of vasomotor tone or to remove vasomotor tone at the time the examination is made.

The significant part played by vasomotor tone is illustrated by comparing the physical signs in a limb (a) when there is normal vasoconstriction, and (b) when there is full, normal vasodilatation. When a person feels chilly he usually has a cold, pale foot, and the veins are small and the pulses small or indistinct. When the same person feels warm the feet are warm and pink, and the veins and pulses are prominent.

An example of such a change in the appearance of vascularity is afforded by comparing the two normal feet of a subject after block of the right lumbar sympathetic ganglia with novocain. The left foot is pale, cool (skin temperature 22° C.), and moist; the veins are small, the arteries small, the pulses fine, and the oscillations one space (aneroid sphygmomanometer). Blanching on elevation is complete in 10 seconds, and color returns to the foot and the small veins fill only after forty seconds of dependency. The right foot is bright pink, warm (skin temperature 34° C.), and dry. The veins are large (diameter 3 times those of left), the arteries large (diameter about 2 times those of left), and the pulses are more readily felt than those on the left. Oscillations are two spaces and blanching on elevation is incomplete, and the color returns and the veins fill after three seconds of dependency.

The diagnostic tests which most capably control the factor of variable vasomotor tone are the so-called vasodilatation tests. In these tests, vasomotor tone is either inhibited reflexly or depressed by an anesthetic. After vasodilatation is initiated it continues to its maximum if the conditions of its initiation are maintained. The resulting blood flow equals the undamaged circulation plus the collateral circulation. The collateral,

that is, the nonpulsatile circulation, can then be estimated by comparing this blood flow with the degree of damage estimated from absent pulses and decreased oscillations (see Fig. 4). Vasodilatation tests can measure even a slight decrease in circulation, and measure the circulation in the more distal tissues, where, in patients with peripheral arterial diseases, the ischemia is usually most severe.

As a rule the rate of blood flow in these tests is estimated clinically by measurements of surface temperature. Skin temperature is conveniently measured by means of a thermocouple or skin thermometer.⁴ A radiometer is less applicable to the small areas of skin on the tips of digits.⁵ Experimentally, plethysmographic and calorimetric methods of measuring peripheral blood flow are used.^{6, 7, 8, 9, 10}

A vasodilatation test is performed in the following manner. The patient reclines, lightly clad, in a cool room, preferably in a constant temperature room at 20 degrees C. The feet, or hands, depending upon which are to be studied, are exposed to room air throughout the test. Digital skin temperature is taken at ten-minute intervals, and, when it has decreased to 24-20 degrees C., vasodilatation is reflexly induced by one of several methods. Vasodilatation begins within a few minutes to an hour, depending upon the method used to elicit it. In the normal subject, when vasodilatation is complete the skin temperature of the digits will rise to a level between 31 and 34 degrees C. The methods for inducing vasodilatation include reflex heat,^{11, 12, 13, 14, 15, 16} artificial fever,^{17, 18} ingestion of alcohol,¹⁹ posterior tibial or ulnar nerve block with procaine,^{20, 21, 22, 23} spinal anesthesia,^{22, 24, 25} general anesthesia, and injection of the lumbar thoracic ganglion with procaine.²⁰ Heat cannot, of course, be applied directly to the extremity which is being studied. The skin temperature rises more rapidly in response to anesthetization of the sympathetics than to other procedures, and to a slightly higher level (about 2 degrees C.) because of the lack of sweating and perhaps other factors. With full vasodilatation the temperature of the fingers is normally one or two degrees higher than that of the toes.

The choice of one rather than another means of inducing vasodilatation in the extremities depends upon the subject, and, to some extent, upon the syndrome presented. In any case, the method chosen must produce vasodilatation; if it fails, another method is selected (see Table IV). For the first trial we choose reflex heat because it is innocuous, simple, and is effective in about 90 per cent of the cases. Satisfactory vasodilatation is produced by applying heating pads to the extremities which are not being tested, and covering the body with blankets.*

Landis and Gibbon^{11, 12} immersed the extremities which were not being tested in water at 45 degrees C. Water immersion is cumbersome, but is

*Pickering has shown that heat applied to a part of the body induces vasodilatation elsewhere by raising the temperature of the blood (ref. *Heart* 16: 115, 1932). Presumably the "vasomotor center" responds to the rise in blood temperature, and lessens vasomotor tone.

even more effective than heating pads in initiating vasodilatation. If reflex heat fails to induce a rise of at least 2 degrees C. in skin temperature, one cannot be sure that vasomotor tone has been abolished, and, although some abnormal vasoconstriction is indicated by this failure, either peripheral nerve block, spinal anesthesia, general anesthesia, or procaine injection of sympathetic ganglia is resorted to. Otherwise, no estimate of the degree of arterial occlusion is gained. When some means other than reflex heat is required (about 10 per cent of the cases), any one of the second choices is nearly always successful in producing maximum vasodilatation.

Vasodilatation tests are, for the most part, easily interpretable (see Table V). Strictly speaking, the interpretation applies solely to blood flow in the skin under the thermocouple, but this is usually representative of surrounding tissues. With a cool room temperature, a rise in skin temperature to 31 degrees C. means that the flow of blood is equal to that of a normal person with full vasodilatation. This level is reached in a limb with no arterial occlusion, or with arterial occlusion which has been completely compensated for by collateral circulation. A rise which falls short of the 31 degrees C. level indicates arterial occlusion—more if the rise is slight, less if the skin temperature approaches 31 degrees C.

Vasodilatation tests are useful (1) in diagnosing or helping to estimate arterial vasoconstriction, (2) in diagnosing early arterial occlusion, (3) in quantitating all but the most severe grades of occlusion, (4) in helping to measure the collateral circulation, and (5) in measuring the capacity for vasodilatation, and hence in deciding about the propriety of vasodilatation therapy, such as sympathectomy. The tests are useful because they remove that important variable, vasomotor tone. They are not indicated in the most severe grades of uncompensated occlusion, for clinical signs and the histamine test afford all of the necessary information in these cases.

TESTS OF ABNORMAL VASOCONSTRICTION

Vasoconstriction is a normal, reversible, physiologic process which controls the blood flow to various tissues in accordance with the total economy of the body. Contraction of blood vessels is produced by shortening of the smooth muscle fibers of the media in response to sympathetic nerve impulses or circulating substances.

Before discussing tests for vasoconstriction, it will be necessary to define certain terms. "Normal vasoconstriction" is the degree of contraction of blood vessels which results from physiologic stimuli. It is not sufficiently intense to interfere with tissue nutrition and does not produce signs or symptoms of ischemia. The cool hands of a subject who is exposed to a cold environment illustrate "normal vasoconstriction."

TABLE V
INTERPRETATION OF VARIOUS VASODILATATION TESTS

PROCEDURE	LEVEL OF SKIN TEMPERATURE RESULTING FROM PROCEDURE	CONCLUSIONS
1. Heat applied to the arms (to test toes); or to legs (to test fingers).	(a) Rapid rise to normal level (31.0° C. or above).	Normal blood flow. (If any occlusion it has been compensated for by the formation of collaterals. Test sufficient.)
	(b) Delayed rise to normal level.	Moderate abnor. vasocon. (Test sufficient.)
	(c) Partial rise, to below normal level.	Effects of organic occlusion, advanced if only slight rise. (Test sufficient.)
	(d) No rise or continued fall.	Abnor. vasocon., but organic occlusion may also be present, so resort to procedure 2, 3, or 4.
2. Posterior tibial (or ulnar) nerve block (to be used only after 1d).	(a) Rise to normal.	*Abnor. vasocon. (If any occlusion it has been compensated for by formation of collaterals. Test sufficient.)
	(b) Partial rise to below normal (in presence of numbness indicating successful injection of nerve).	*Mixture of abnor. vasocon. and occlusion (more rise indicates less occlusion, test sufficient).
	(c) No rise, or continued fall (in presence of numbness, etc.).	*Abnor. vasocon., but organic occlusion probably also is present, so resort to procedure 3, or 4.
3. High spinal anesthesia (applicable only for leg symptoms).	Same as 2.	*Same as 2.
4. Novocain injection of sympathetic chain (lumbar or dorsal).	Same as 2.	*Same as 2.

*Routinely only the group 1d is chosen for procedure 2, 3, or 4. If patients previously untested are chosen for procedure 2, 3, or 4, conclusions should be as under 1.

"Abnormal vasoconstriction" is an excessive contraction of blood vessels in response to physiologic stimuli, or contraction as a result of abnormal stimuli. The vasoconstriction is sufficiently intense to interfere with the normal metabolic demands of the tissues and produces signs and symptoms of ischemia. The results of abnormal vasoconstriction are, usually, coldness, cyanosis, and pain, and, ultimately, superficial necrosis. "Abnormal vasoconstriction" is frequently seen in association with organic vascular occlusion, as in thromboangiitis obliterans.

"Vasospasm" is a term which has been loosely used to indicate abnormal vasoconstriction. It seems to us that it should be used specifically to denote an actual spasm of blood vessels, with complete circulatory arrest. The classical manifestations of vasospasm occur in the blanched fingers of patients with Raynaud's disease. It may also follow arterial trauma, as in acute embolism of peripheral arteries, and is occasionally seen in patients with acute iliofemoral thrombophlebitis. Prolonged spasm, although rare, will cause gangrene.

"Capacity for vasodilatation" is the measured increase in circulation which occurs when vasoconstrictor tone is removed, as it is in one of the vasodilatation tests. It does not necessarily mean that "vasospasm" or "abnormal vasoconstriction" is present, but simply indicates that the blood vessels have an increased capacity when the vasoconstrictor tone is removed. Some capacity for vasodilatation is a prerequisite for a diagnosis of normal or abnormal vasoconstriction or vasospasm.

TESTS OF VASOCONSTRICTION

With these definitions in mind, vasoconstriction is revealed clinically by intermittent coldness, blanching, or cyanosis, and is frequently associated with excessive sweating, or pain, in a limb which has its pulses and at least some capacity for vasodilatation. No tests have been devised to differentiate between normal and abnormal vasoconstriction and vasospasm. If the patients are free from symptoms at the time of examination, exposure to cool air or the immersion of an extremity in cold water may help establish the diagnosis of abnormal vasoconstriction. When vasodilatation produced by reflex heat fails to relieve vasoconstriction, and relief is obtained by more vigorous procedures such as anesthetization of sympathetic nerves, the patient can be said to have abnormal vasoconstriction, but there are other patients with undoubtedly abnormal vasoconstriction who obtain prompt relief from reflex heat.

Vasoconstriction produces ischemic symptoms which are indiscernible from those of organic arterial occlusion. The vasodilatation tests play an important part in the study of various grades of vasoconstriction, in that they measure the capacity for vasodilatation, thereby excluding, or measuring the degree of, organic occlusion. It is most difficult to differentiate vasoconstriction from occlusive vascular disease when the latter is accompanied by abnormal vasoconstriction. In such cases, careful attention to the history, examination, and vasodilatation tests gives a remarkably accurate picture of the abnormal vascular system.

OSCILLOMETRY

Clinical oscillometry affords a measure of the total pulsation transmitted by the heart's beat to the vessels encompassed by the oscillometer cuff.^{26, 27} In normal subjects, arteries large enough to carry a palpable pulse contribute most of the pulsation, and the smaller arteries and arterioles make up the rest. Aside from alterations in the strength or rhythm of the heartbeat, the oscillometric readings in a limb become abnormal because of several common disturbances in the peripheral arterial circulation. The oscillations are lessened (1) by obstruction to the pulse wave, such as that caused by arterial occlusion and aneurysm, even in the presence of an adequate collateral circulation, and by arterial or arteriolar spasm, (2) by lessened flexibility of arteries and arterioles, such as occurs in arteriosclerosis, (3) by a diminution in the size of the arterial, arteriolar, and probably venous bed, (4) by a profound decrease

in blood pressure, and (5) by an inflexible, tight skin such as that of scleroderma. The oscillations are increased (1) by vasodilatation, whether it be physiologic or pathologic, and (2) by escape of arterial blood directly into veins, as with single or multiple arteriovenous fistulas.

Great fluctuations in blood flow, such as are induced by cold and heat in the skin, and by rest and exercise in muscle, change the oscillometric readings. In a normal subject with peripheral vasoconstriction oscillometric readings from a finger are increased about sixfold, from a toe about threefold,³ and from the ankle about twofold when full peripheral vasodilatation is induced by heat. Oscillometric readings from the resting calf are about doubled immediately after exercise, in spite of a concomitant slight decrease in the blood flow through the skin of the calf. Therefore, if minimal oscillations are rated as 0, and maximal normal oscillations as 1, the range of normal at ankle level is between $\frac{1}{2}$ and 1 when the subjects are under controlled conditions with respect to exercise and warmth. The amplitude of the oscillations is more nearly standardized when measurements are made only after vasomotor tone is released, or when, in a single subject, readings are compared at identical levels of the two legs. Slight discrepancies in adjustment of the cuff still contribute some error. Muscle spasm, anomalous arteries, cardiac weakness, severe scleroderma, and the size of the subject rarely confuse the interpretation.

The clinical use of oscillometry is most helpful (1) in ascertaining the exact level of arterial occlusion, (2) in helping to establish the presence or absence of pulses which are not palpable because of overlaid muscle, fat, or edematous tissue, (3) in measuring past vascular damage which may or may not have been compensated for by a nonpulsatile collateral circulation, (4) in detecting the site of arteriovenous fistulas, and (5), when combined with a vasodilatation test in estimating the extent of the collateral circulation (when collateral circulation equals blood flow minus undamaged circulation).

Several types of oscillometers are available for clinical use; in all of them the pulsations are transferred from a cuff to a tambour with a recording needle. A recording instrument has the advantage of producing a permanent record. The ordinary aneroid sphygmomanometer is a nonrecording form of oscillometer which is satisfactory for most purposes. With this instrument the normal reading at the ankle is between one and two scale markings, when each marking indicates 2 mm. Hg. Similar instruments which are marketed as oscillometers have larger and more easily read scales.

CUTANEOUS HISTAMINE REACTIONS

Unless there is marked cutaneous vasoconstriction, histamine, when introduced into the skin of a normal person, produces a localized wheal within three minutes after injection. If the blood flow to the part has been completely arrested no wheal appears.²⁸ If the blood flow is greatly

decreased, either the wheal will not appear or its appearance will be delayed.^{29, 30} Starr has utilized this phenomenon as a measure of blood flow. Any delay in wheal formation of more than five minutes indicates severe ischemia. When no wheal appears the life of the tissues is endangered, and gangrene is usually imminent unless blood flow can be made to increase. Moderate grades of occlusive disease fail to alter the time of appearance of the wheal.

This test, like the vasodilatation test, is a test of capacity for cutaneous blood flow only, but this is hardly a limitation because failure of the cutaneous circulation is the cause of most of the more serious consequences of peripheral vascular disease. The histamine test is more sensitive than the vasodilatation test only in the lowest range of blood flow estimated by the latter.

The test is performed by placing a small drop of 1/1,000 histamine acid phosphate on dried, cleaned, nonedematous skin (preferably not over bone), by needling the skin several times through the drop, and by feeling for a wheal.* Any palpable irregularity is considered a satisfactory wheal. A necessary precaution is that vasoconstriction be relieved before this test for arterial occlusion is performed; a cold, white, or blue skin should be prepared by gentle warming. There are exceptions in Raynaud's disease and in acrocyanosis, as described below.

The histamine test is indicated mainly when occlusive arterial disease is known to be present. We have never seen a wheal fail to appear within five minutes, when the test was properly performed, in patients who have a fairly good or good cutaneous circulation, as indicated by the vasodilatation test. The reaction is unaffected by moderate degrees of arterial occlusion; the test is sensitive to slight changes in severe arterial occlusion. It is most useful in making a prognosis of the viability of ischemic tissues. Skin which fails to develop a wheal after histamine injection, when the precaution against vasoconstriction has been taken, is too ischemic to enable incisions to heal, whereas delayed wheal formation indicates that healing is improbable. Wheal formation within 3 to 5 minutes indicates that there is sufficient blood flow for the healing of incisions, but infection, because of its great demands on blood flow, can upset conclusions based on the histamine test. The test should not be performed on, or adjacent to, necrotic tissue, but is sometimes most useful a few centimeters above a line of demarcation. The test is sometimes helpful in determining the lowest level at which an amputation wound can be expected to heal, but in this connection Starr has emphasized the need for taking all data available into account in deciding the question whether amputation should be done, and at what level.

The test is useful in differentiating between Raynaud's disease and acrocyanosis. In Raynaud's disease the spasm is predominantly in the small and large arteries, and, in acrocyanosis, in the arterioles. When

*Histamine for this purpose can be kept for months when chloretone is added to make a 1 per cent solution.

histamine is needled into the skin it does not reach the arteries, and so it fails to produce a wheal in the white, cold fingers of a patient with Raynaud's disease. In the ischemic, mottled, red or blue, cold skin of acrocyanosis, histamine produces a brilliant flare and conspicuous wheal. In the presence of peripheral neuritis a flare may not appear, but the wheal is not affected.

Starr has studied the prognostic value of the histamine test on the feet of patients with diabetes. Of eight-nine patients with diabetes who were followed for five years, none with a normal reaction developed any serious vascular trouble. Of the thirty-two patients who gave markedly impaired reactions, eighteen died, and only five survived the five-year period without serious lesions of the feet.²⁹

THE INTRACUTANEOUS SALT SOLUTION WHEAL TEST

Stern and Cohen³¹ adapted to studies of peripheral arterial circulation the test that McClure and Aldrich^{32, 33} used to investigate edema. They found that a wheal which resulted from the intracutaneous injection of physiologic saline disappeared more quickly in markedly ischemic skin than in skin with a normal blood supply. The test is less well standardized and less quickly performed than the histamine test, which appears to have supplanted it.

REACTIVE HYPEREMIA TESTS

Reactive hyperemia, i.e., an increase in the flow of blood above what is normal for the limb, results after relief of temporary circulatory arrest.³⁴ To perform this test the blood is drained out of the foot by elevation, and the little color remaining in the foot is pressed out manually. A blood pressure cuff is then placed around the thigh with the leg in the elevated position, the cuff is inflated to a pressure greater than systolic pressure, and the foot is then lowered to the horizontal position. The blanched appearance of the foot is preserved. Sudden release of the pressure in the cuff results in a rapid flush which is occasioned by inflowing blood, except when there is arterial spasm or occlusion. Lewis and Grant³⁵ and Freeman³⁶ have studied the mechanism of the vasodilatation produced by the ischemia prior to release of the cuff. Pickering³⁷ standardized the conditions which are necessary when the phenomenon is used as a test of arterial occlusion. The foot is warmed in water at 35° C. for ten minutes, and occlusion is then maintained for five minutes. In a limb with normal vessels the flush is complete within three seconds after release of the cuff pressure. The flush is delayed in extremities with occluded arteries in proportion to the extent of the occlusion, and occurs evenly or unevenly, depending upon the distribution of the occlusion. The duration of maintenance of cuff pressure should be lessened when severe arterial occlusion is suspected.

When reactive hyperemia is used to test for arterial occlusion in the upper extremity, the hand is raised, the fist closed, the wrist grasped

tightly by the observer, the hand lowered, opened, and, after three minutes, the wrist released. Heating the hand is less necessary than heating the foot because vasomotor tone is less readily maintained in the hand. The resulting flush is interpreted in the same way as that in the foot. A useful modification serves to demonstrate patency or occlusion of the ulnar artery when the ulnar pulse cannot be palpated. The modification follows the above directions, with the addition that the radial pulse is held compressed from the time the pressure is being released. Care should be taken that compression of the radial be prevented from extending to the ulnar artery. In like manner, occlusion of a single one of the paired digital arteries can be demonstrated. These modifications of the test are occasionally of diagnostic value early in the course of thromboangiitis obliterans.

One of the earliest forms of the reactive hyperemia test is the most complete, and, in its special application, the most useful. Matas³⁸ designed the test to estimate the extent of the collateral circulation in a limb with an arteriovenous fistula prior to operation. The whole circulation is arrested by an Esmarch bandage, and the main artery just above the fistula is compressed digitally or instrumentally to a degree sufficient to occlude it. The bandage is removed while arterial compression is maintained. Reactive hyperemia results through the collateral circulation only. The test demonstrates the extent of the collateral circulation, and, therefore, shows whether or not it is safe to undertake surgical procedures such as ligation and excision. Halstead³⁹ suggested a somewhat similar procedure, in which a metal band is adjusted so that it will partly occlude an artery above an arteriovenous fistula. This procedure is both a test and a therapeutic method. The tightness of the band is repeatedly adjusted to maintain a barely adequate blood flow, thus diminishing the symptoms from the fistula and encouraging growth of collateral circulation without causing undue ischemia. An opportunity is thus afforded for final arterial closure with lessened danger to the limb.^{38, 39}

METHODS OF ESTIMATING BLOOD FLOW THROUGH MUSCLE

(TESTS OF INTERMITTENT CLAUDICATION)

Intermittent claudication results from interference with normal arterial blood flow through muscle. An adequate estimate of muscle blood flow can usually be obtained from the patient's statement concerning the walking distance necessary to precipitate pain, or more accurately by having the patient walk at some standard rate, such as 120 steps per minute.⁴⁰ A satisfactory estimate can be made by having the patient alternately press and raise the foot against a pedal.⁴¹ The most objective method of measuring intermittent claudication in the muscles of the calf is that of Hitzrot, Naide, and Landis.⁴² In the operation of this test the patient reclines, with the foot resting against a board which is supported by a spring. A uniform electrical stimulus

is applied intermittently to the calf muscles, and the resultant contraction is recorded graphically. The record obtained is compared with a normal graph. This method has the advantage over other tests of intermittent claudication in that the record is more objective, and one can, to some extent, subdivide the patient's muscle ischemia into (a) extent of ischemia and (b) intensity of ischemia. Widespread ischemia of large muscle groups results in a very much reduced amplitude of contraction before pain develops. Intense ischemia of a small muscle group results in pain before a significant decrease in amplitude occurs. With this device the stimulus for contraction remains the same when the pain begins. Decrease in contraction results from muscle fatigue.

Claudication tests are of value (1) when patients are unable to give a satisfactory history of intermittent claudication, (2) in differentiating between intermittent claudication, faulty mechanism of an orthopedic nature, neurologic disorders, and neuroses, and (3) in following changes in the severity of intermittent claudication.

PHYSIOLOGIC CONSIDERATIONS

In arterial disease two major processes are at work: (1) obstruction of arteries and (2) development of collateral circulation. Superimposed upon these structural changes are two additional factors, namely, the varying needs for blood flow and reflex vasoconstriction. Only by evaluating the circulation from the standpoint of past damage, its extent and location, previous repair, functional capacity, and superimposed vasoconstriction can the clinical status of each individual patient be entirely appreciated.

Tests of the peripheral circulation can be divided into two general categories: (1) Those which measure previous damage, i.e., past occlusion (oscillometry, careful palpation of pulses, arteriography,⁴² and perhaps blanching of the limb on elevation) and (2) those which measure blood flow, e.g., reactive hyperemia tests, various vasodilatation tests, and the histamine wheal test (see Table IV). It must be emphasized that past arterial damage is by no means necessarily synonymous with present functional defect. A comparison of the results of two of the tests for past damage (i.e., oscillometry and palpation of the pulses) with the results of two tests of present function (i.e., the reflex vasodilatation test and the histamine test) illustrates this fact.

In Fig. 1, digital blood flow, as measured by the air plethysmograph, is plotted against the temperature of the adjacent digit. The normal variability of digital blood flow is shown in terms of both blood flow and skin temperature. The values are taken at random from fifteen normal subjects. During marked vasoconstriction, normal digital blood flow is as low as 1 c.c. of blood per 100 c.c. of tissue per minute, and during vasodilatation as much as 100 times that amount. In a cool room the skin temperature of a normal finger varies from 20 to 34 degrees, depending upon the rate at which blood is flowing.

Fig. 2 shows the clinical significance of the skin temperature of digits with maximal vasodilatation and a room temperature of 21° C. (70° F.), and illustrates the capacity for vasodilatation within the digits. The normal skin temperature, with maximal vasodilatation, of a toe is about 31° C. At 29° the skin temperature is subnormal but "good"; at

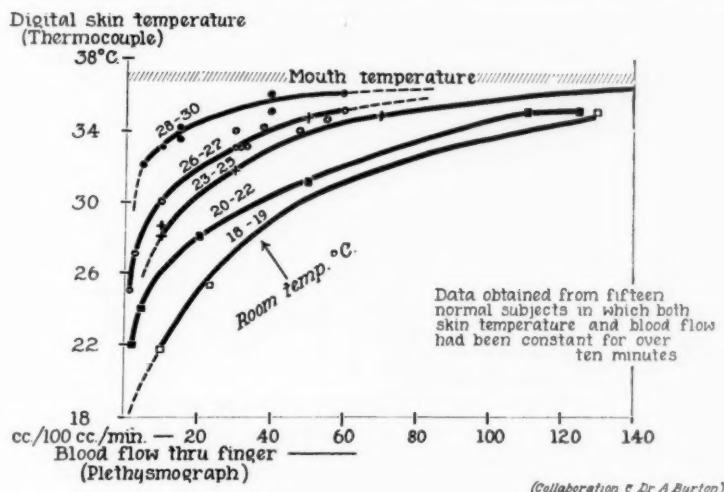


Fig. 1.—Relationship of digital skin temperature to blood flow through adjacent finger.

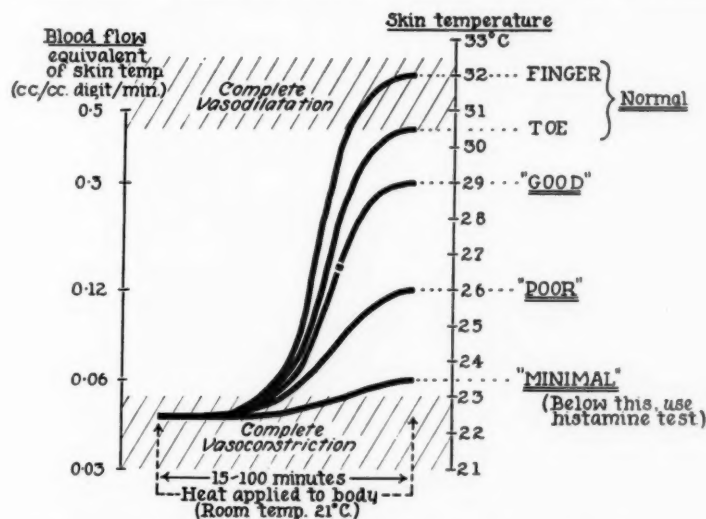


Fig. 2.—Clinical significance of digital skin temperature.

23° it is "minimal," and gangrene is imminent. With this low capacity for vasodilatation, and here only, the histamine wheal test offers a finer differentiation of functional capacity.

By and large, oscillations and pulses are closely similar measurements of past damage. Fig. 3 illustrates this relationship. Ankle pulses are plotted against oscillations at the ankle. Absent pulses and minimal

oscillations and normal pulses and maximal oscillations correspond well. Neither oscillometry nor pulses, however, necessarily indicate functional capacity. In Fig. 4 ankle pulses are plotted against digital skin temperature when there was maximal vasodilatation in the toes.* Although with severe, uncompensated occlusion there are usually no pulses and

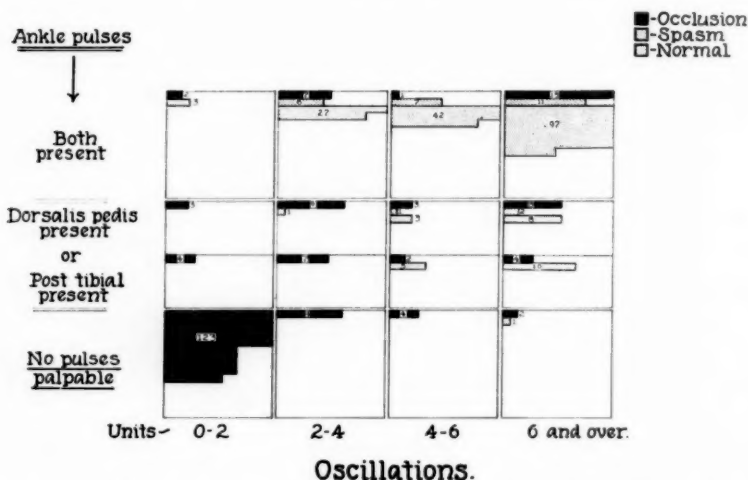


Fig. 3.—Relationship of ankle pulses to oscillometric readings. Each large square represents 200 legs.

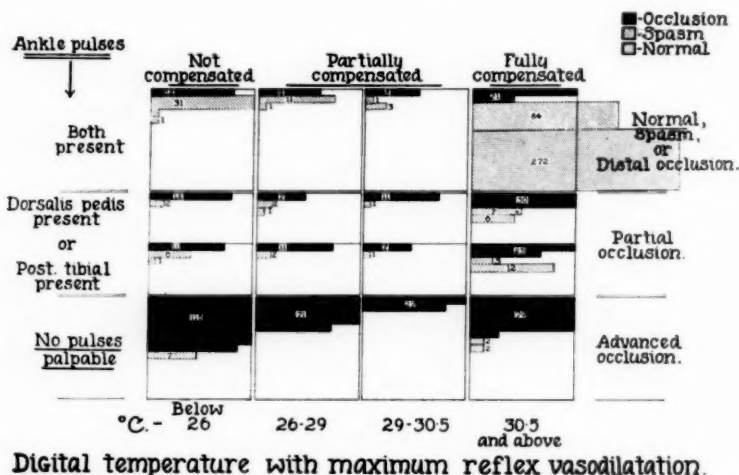


Fig. 4.—Relationship of ankle pulses to capacity for vasodilatation. Each large square represents 200 legs.

a low skin temperature, and normal limbs usually have both ankle pulses and a high skin temperature, there were 176 limbs in which there were no pulses and yet considerable blood flow. These observations are interpreted as evidence of fair to excellent function of a nonpulsatile

*A graph of oscillations versus skin temperature with maximal vasodilatation has been omitted because it is essentially the same as that of pulses versus skin temperature.

collateral circulation. Other points which fall out of line with good pulses but lessened function are interpreted as abnormal vasoconstriction* or distal occlusion. The data on nonpulsatile collateral flow are again presented in Fig. 5. This figure shows the results obtained from the vasodilatation test on all limbs in which no ankle pulses were felt. The

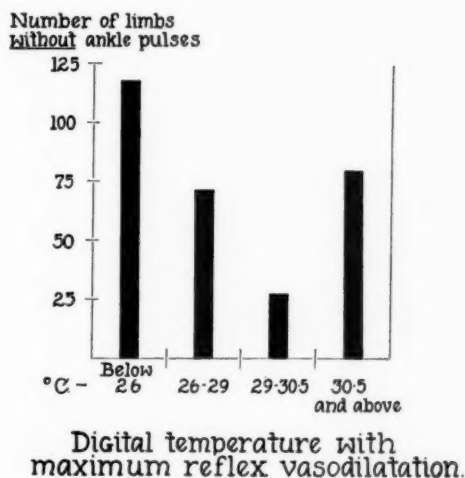


Fig. 5.—Vasodilatation test in patients with arterial occlusion.

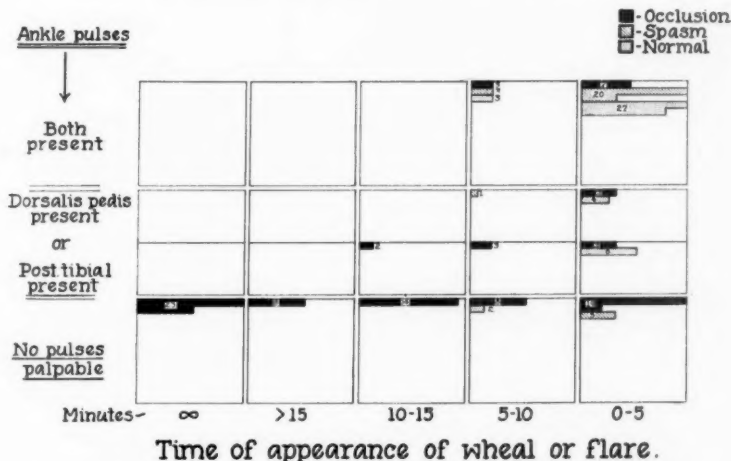


Fig. 6.—Relationship of ankle pulses to histamine test. Each large square represents 200 legs.

largest group of these limbs had poor function, but there were three other large groups in which the function was fair or even excellent, showing the great frequency with which a collateral circulation follows severe damage.

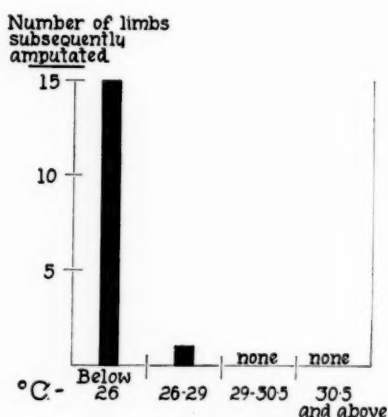
That the pulse wave does not necessarily indicate the functional

For simplicity in Figs. 2, 4, and 6, "abnormal vasoconstriction" has been termed "spasm."

capacity of the vessels is shown also in the graph of histamine test versus ankle pulse (Fig. 6).

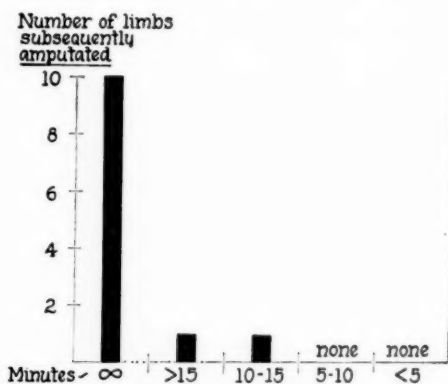
The prognostic significance of the vasodilatation test and of the histamine test is shown in Figs. 7 and 8. Amputation is seldom required if the vasodilatation test or the histamine test shows good function.

A structural and functional classification of conditions of the peripheral arteries is presented in Table II. Prognosis and therapy follow principles already indicated, but are of course influenced by knowledge gained from the history, physical examination, conventional diagnosis, and a knowledge of the metabolic needs of the peripheral tissues. Especially if there is a lesion, the metabolic needs may determine prognosis quite as much as does the capacity for blood flow.



Digital temperature with maximum reflex vasodilatation.

Fig. 7.—Clinical significance of vasodilatation test.



Time of appearance of wheal or flare.

Fig. 8.—Clinical significance of histamine test.

SUMMARY

In peripheral arterial disease there are two major processes at work: (1) obstruction of arteries and (2) formation of collateral circulation. Either damage or repair may become dominant. Collateral circulation means functional repair. Vasodilatation tests, the histamine test, and reactive hyperemia tests are tests of function, and when past vascular damage is estimated by oscillometry or palpation of pulses these tests help to estimate the extent of the collateral circulation. Superimposed abnormal vasoconstriction may confuse the picture. Only by evaluating the circulation from the standpoint of past damage, its extent and location, repair, functional capacity, and superimposed vasomotor tone can the clinical status of each individual patient be entirely appreciated. Various tests of peripheral arterial conditions are important adjuncts to information gained from a complete history and physical examination.

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DISCUSSION

DR. NELSON W. BARKER (Rochester, Minn.).—I think that this presentation is an excellent statement of the problem of study in cases of peripheral vascular disease. Two comparatively simple tests were not discussed: (1) The claudication test, which can be done in several different ways, either with apparatus or by having the patient take a fixed number of steps per minute under standard environmental conditions in order to ascertain the time necessary for claudication to develop. This is a test of the functional capacity of the circulation of the muscles, whereas most of the other tests measure the functional capacity of the circulation of the skin. (2) The elevation-dependency test, the value of which I would like to emphasize. This requires no apparatus, but should be done under controlled environmental temperatures, and, when comparative tests are made, they should be done at the same time of the day and at the same time after ingestion of food. The patient's feet should be elevated for a fixed period until maximal blanching has occurred; then the feet are rapidly placed in the dependent position, and the time required for

the color to return is recorded. This simple test gives considerable information as to the functional capacity of the circulation of the skin of the feet.

I would like to emphasize another fact which has some bearing on prognosis. Arterial insufficiency of considerable degree which has come on rapidly may be a much greater hazard as far as the development of gangrene is concerned than the same degree of arterial insufficiency which has come on gradually or has been present for a considerable period of time. The tissues may develop a capacity to exist under conditions of considerable ischemia if it does not develop too rapidly.

DR. D. W. KRAMER (Philadelphia).—I was pleased to hear Dr. Montgomery's paper. I think circulatory function tests have now reached the point where they are considered as necessary procedures in diagnosing peripheral vascular disorders.

It is now generally recognized that a history and an examination of the peripheral pulses are not sufficient because the patient may have a good dorsalis pedis pulse and still have gangrene. On the other hand, the dorsalis pedis pulse may be absent even when the patient has an efficient circulation.

There are about thirty tests which may be employed. Some of them are more practical than others. Some are prohibitive because of their expense and can only be employed in hospitals and clinics.

I was glad to hear Dr. Montgomery discuss the oscillometer. This method of studying the circulation has been unduly criticized. Although it has its drawbacks, it does give definite information, particularly pertaining to mass pulsation of the larger vessels.

The histamine test is a simple procedure that is inexpensive and can be performed in the office. It gives us definite information as to the capillary response and, indirectly, the condition of the underlying vessels.

Calorimetric and thermometric studies are helpful in deciding whether we are dealing with organic occlusive conditions or vasospasm. However, all of these tests still require checking up and further investigation.

Even our views concerning skin surface temperature studies, which we accept as our most reliable method, may some day require modification. At the present time I have two patients who apparently have the classical clinical manifestations of thromboangiitis obliterans, but their skin surface temperature can be made to rise to maximum limits. This would indicate that we were dealing entirely with vasospasm, but I doubt whether this was true in these particular cases.

I hope that others will continue to investigate the various circulatory function tests and help establish their value in interpreting the various pathologic disorders of the peripheral circulatory system.

DR. HUGH MONTGOMERY (Philadelphia).—There is, of course, a long list of tests. We started out to discuss approximately twenty-five of them, but saw that this was impossible.*

Certainly the claudication test has considerable value, although I think not as much as some of the others, because walking alone will give very good information concerning the function of the calf or foot muscles, except in unusual circumstances.

I do not altogether agree with Dr. Barker that the elevation and dependency test is fairly accurate. We look on it more, I think it is fair to say, as a part of the physical examination. Very useful information can be gained from it, as it certainly can be from the physical examination in general, and we are not trying in any way to leave the impression that these tests take the place of a thorough physical examination.

I was wondering whether Dr. Kramer's patient was not one who did have thromboangiitis obliterans, but nevertheless had perfectly normal function—in other words, a patient who had obtained his collateral circulation.

*This paper was shortened for verbal presentation and now is presented in full.

Department of Clinical Reports

PAROXYSMAL TACHYCARDIA IN INFANCY

REPORT OF CASE

L. FLOYD HOBBS, M.D.

ALEXANDRIA, VA.

PAROXYSMAL tachycardia in infancy is a relatively rare condition. The youngest patient with this condition, reported by Werley,¹ was an infant 4 days old. Doxiades² has reported a case in a 7-day-old infant. Farr and Wegman³ reported a case in a 24-day-old infant, and Colgate and McCulloch⁴ in a 3-week-old infant. Von Bernuth and von den Steenen⁵ observed the condition in a 3-week-old child; Schuster and Paterson⁶ reported two cases, one in an infant 9 weeks old and another in an infant 2 months old. O'Flynn⁷ reported a case in an infant 8 months old, and Koplik⁸ a case in an infant 22 months old. Lyon⁹ also reported a case in a child 31 days of age. Reports of cases occurring in children over the age of 2 years are more numerous. Taran and Jennings¹⁰ have cited fifty-two cases occurring in infants and young children. Clark¹¹ has also cited many cases in older children.

The etiology of paroxysmal tachycardia is obscure. In some cases post-mortem examinations have revealed definite cardiovascular changes, while in other cases there have been no demonstrable changes. In several cases the tachycardia was apparently the result of or a sequela of an organic disease such as encephalitis, chorea, or muscular dystrophy. Again the attacks ran concurrent with or followed such conditions as measles, whooping cough, or other infectious diseases. In some cases congenital heart conditions apparently acted as causative factors. However, it has been frequently noted that many of these attacks followed a mild upper respiratory infection.

The main purpose of this paper is to report a case of paroxysmal tachycardia in an infant 2 months old.

This patient, a white male, was the firstborn of a 34-year-old mother. He was delivered by medium forceps following a long labor. The child's condition was good at the time of birth. Two weeks following birth the child was examined by a pediatrician, who found no evidence of birth injuries nor of any congenital anomalies.

The patient was seen on March 8, 1938, at 9:00 P.M., and was diagnosed as having a very mild sore throat. The temperature was 99.6° F. by rectum. The heart rate was too rapid to count. There was no evidence of cardiac failure at this time. The following morning the child was seen again, and at this time he still had a very rapid heart rate. There was definite enlargement of the liver, and the spleen

Received for publication March 20, 1940.

could be palpated. There was very little cyanosis. The patient was hospitalized on March 9, 1938. On admission, oxygen was started, and morphine sulfate, $\frac{1}{150}$ gr., was given every four hours. Pressure was applied to the vagus nerve and to the eyeball, without any slowing of the heart rate. Vomiting was induced with ipecac, but this too failed to stop the tachycardia.

An electrocardiogram showed a regular rate of 291 per minute. A teleroentgenogram of the chest did not show any enlargement of the heart. The urine and results of other laboratory tests were well within the limits of normal. Since the child refused nourishment, a hypotonic solution of glucose was given intravenously.

On the following day (March 10) there was very little change in the patient's condition. He refused his feedings but took water in small quantities. At 2 o'clock in the afternoon the patient was given 10 minims of digifolin subcutaneously. Two hours later the dose was repeated. At 5:30 P.M., the heart rate dropped to 140 per minute, and the patient's general condition improved. He began to take his feedings, and he was dismissed from the hospital on the following day. Apparently he had recovered completely.

On March 25, seventeen days following the initial attack, the child had another attack. He was given 10 minims of digifolin shortly after the onset, and this dosage was repeated every eight hours. The heart resumed its normal rate on March 27, after three doses of digifolin. The third attack occurred thirteen days after the second; again digifolin was given, and the heart returned to normal in twelve hours' time. On April 10, three days later, there was another attack which lasted sixteen hours and required two doses of digifolin. Ten days later another attack occurred which lasted twenty-four hours. Four doses of digifolin were given before the rate returned to normal. The sixth attack occurred forty-seven days later and lasted twenty-four hours. At this time two doses of digifolin were given. The seventh attack began July 29, or thirty-seven days later, at 3:30 P.M. We did not use digifolin until the next day at 12:45 P.M. The heart rate dropped to 175 per minute in an hour and slowed to 140 in another hour.

Since this last attack, the child has been free of the irregularity. At this time, almost two years later, he is apparently healthy and even more vigorous than the average child of 2 years.

The treatment of paroxysmal tachycardia has been extremely varied. Some clinicians have used oxygen, digitalis, morphine, quinine bisulfate, and quinidine. In certain cases quinidine therapy apparently exaggerated the condition. Several cases have resulted in death, regardless of treatment. Other cases have ended spontaneously. Shookhoff, et al.¹² used digitalis, phlebotomy, quinidine sulfate, and quinine urea hydrochloride in their case, without result. Later, however, when decompensation occurred, the child responded to digitalis. Farr³ and Van Cleve¹³ reported cases in which digitalis was of benefit. Meeholyl has been used by Wright,¹⁴ with good results. This treatment was suggested in our case, but we were under the impression that this drug was rather dangerous in infancy. I believe that digitalis is probably the best drug to use in this condition. Certainly it is the best drug for patients who show any signs of cardiac decompensation.

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VEGETATIVE ENDOCARDITIS IN AN AURICULAR SEPTAL DEFECT

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"VEGETATIONS, while common on the margins of the interventricular septal defect, patent ductus or malformed valvular orifice, almost never occur on the interauricular septum." This constitutes a recent statement of Maude E. Abbott¹ in a personal communication. In her series of 850 cases of congenital cardiac anomalies, only one case, and that a case of subacute bacterial endocarditis upon a lower auricular septal defect, was found. This rarity has also been stressed by White.² No report of a substantiated case of an acute process with fresh vegetations has been found by the author. For these reasons, the following report of a very unusual pathologic picture is presented.

During the progress of experimental investigations upon resection of the lower third of the esophagus, an apparently healthy female dog was used. The estimated age of the dog was 4½ years, and the weight was 20.4 kg. For two weeks prior to operation the animal had been observed in the isolation room, and although no cardiac studies had been carried out, the animal was considered to be in good health. Daily records are made of the pulse rate, rectal temperature, and respiratory rate of dogs subjected to this experimental procedure, in order that a true preoperative base line can be found for postoperative comparison. The results in this case fell within what was considered to be the normal for such dogs: temperature, 100.8 to 102.6° F.; pulse, 90 to 120; respirations, 18 to 24.

Under combined morphine and nembutal anesthesia, a resection of the cardiac end of the stomach and the lower third of the esophagus was performed. During this transthoracic procedure, the cardiac action could be directly observed and was not unusual. No direct pericardial or cardiac injury was occasioned by the operation. No untoward effects from either the anesthesia or the operation were noted, and within twenty-four hours the animal was again in apparently good health. The postoperative course remained smooth and uncomplicated until the fourth postoperative day when the rectal temperature rose to 103.2° F. from a previous level of 101.6 to 102.4° F.; respirations rose from 24 to 36, and pulse from 120 to 130. Roentgenograms and physical examination of the chest corroborated the impression of atelectasis in the lower lobe of the left lung. Diagnostic aspiration of the pleural cavity was negative. Following hyperventilation, the clinical findings disappeared within a few hours, and the course remained uneventful until the eighth postoperative day, when a slight wound infection was found. This persisted in mild degree until the dog's death, fourteen days following operation. A precipitous drop in temperature to 99.6° F., without change in pulse or respiration, occurred on the tenth postoperative day. The pulse gradually increased from then until the thirteenth postoperative day, as did also the rectal temperature and respiratory rate. The clinical impression of auricular fibrillation and marked general toxicity was noted on the thirteenth postoperative day, and the animal was found moribund the morning of the fourteenth postoperative day.

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Received for publication March 22, 1940.

At autopsy, a mild infection of the lower end of the chest wound was found, but the operative area showed primary healing of the anastomosis, without perforation or stricture. Both pleural cavities were free of fluid and exudate, but the presence of multiple petechiae scattered diffusely about the periphery of the lungs was noted. There was no gross pneumonia but a marked, diffuse pulmonary edema. The right ventricle of the heart was considerably dilated, and on opening of the pericardium, it was evident that intravascular clotting had occurred recently in the descending branch of the left coronary artery (Fig. 1). An antemortem thrombus was found on opening this vessel. Infarction was demonstrated by the discoloration of the surrounding 2 cm. of myocardium and by the small



Fig. 1.—Area of denuded epicardium and infarction about the left descending coronary artery. Some small petechiae can be seen on the specimen of the lung.

area of denuded epicardium overlying this area. Thirty cubic centimeters of blood-tinged fluid was found in the pericardial cavity. On opening the heart, no mural thrombi were found, but an interauricular septal defect, as shown in Fig. 2, was discovered. This consisted of an opening 6 mm. in diameter, and at its edge on the left auricular side three fresh, globular vegetations were present. Scattered smaller vegetations were found along its intraseptal course. The remaining cardiac chambers, as well as the great vessels, showed no abnormalities either as to position, diameter, or configuration. The valvular structures throughout were delicate and apparently competent. Gross evidence of embolic phenomena were easily discernible

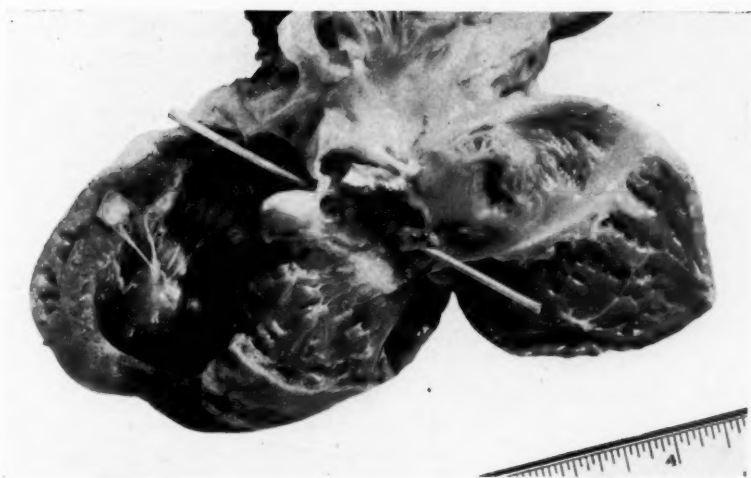


Fig. 2.—Interauricular communication through which a probe is passed, and the fresh vegetations about one orifice.

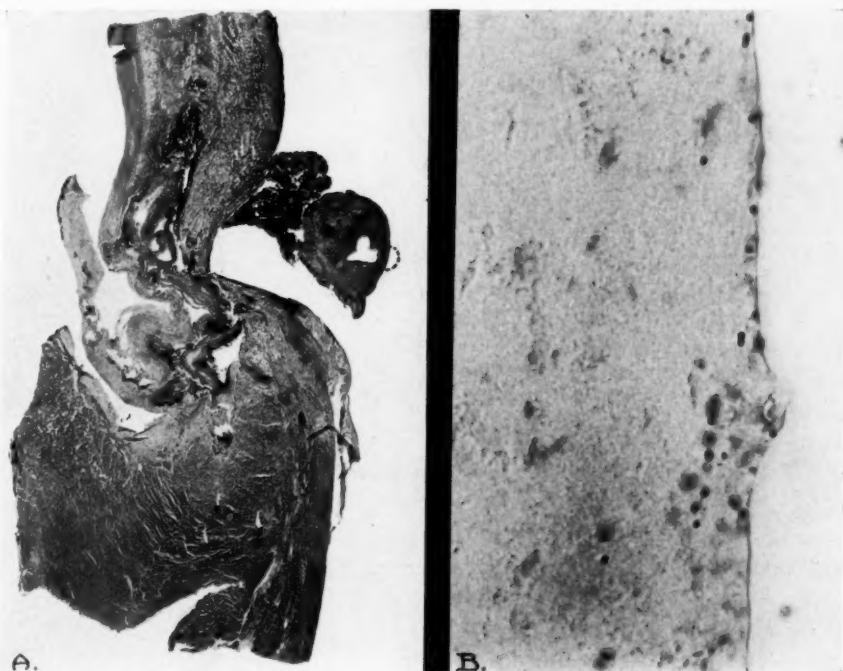


Fig. 3.—*A*, Photomicrograph of section taken through area of the septal defect, showing interauricular and interventricular septa. Portions of valves and large vegetations are seen. This section is oblique to the channel and shows only the opening on the left auricular side. The lowest portion of the interauricular septum is distorted by technique in cutting. ($\times 15$.)

B, Photomicrograph of area inclosed by circle in *A*, demonstrating organisms, fibrin, and platelets. ($\times 1200$.)

on the cut surfaces of all lobes of the lungs, in the right cerebral cortex, the parenchyma of both kidneys, the cortex of the right suprarenal gland, and the spleen.

It is unfortunate that no cultures of the fresh tissues were made, but microscopic study of the involved organs revealed multiple septic infarcts, and on bacteriologic study, large groups of a gram-positive diplococcus were found. Sections for microscopic study made through the infarcted area about the left coronary artery showed evidences of fresh infarction with polymorphonuclear leucocytic infiltration about groups of bacteria similar to those previously described. Sections through the interauricular septum revealed a peripheral area of fresh abscess formation, as well as considerable deposits of fibrin, groups of platelets, and bacteria in the vegetations themselves (Fig. 3, *A* and *B*).

CONCLUSIONS

A case of a dog with postoperative acute bacterial endocarditis superimposed upon a congenital interauricular septal defect is presented. Embolic manifestations of a paradoxical nature occurred. The extreme rarity of this complication and the possible interest to other investigators prompted this report.

REFERENCES

1. Abbott, Maude E.: Personal communication.
2. White, Paul: Heart Disease, ed. 2, New York, 1937, Macmillan Co., pp. 307, 472.

Department of Reviews and Abstracts

Selected Abstracts

Chen, K. K., and Elderfield, Robert C.: The Cardiac Action of the Derivatives of Strophanthidin and Cymarin. J. Pharmacol. & Exper. Therap. 70: 338, 1940.

A few derivatives and isomers of strophanthidin and cymarin have been studied in frogs and cats with the aim of determining the relative importance of chemical groupings present in nature.

Strophanthidin is about one-fifth as active in frogs and one-third as active in cats as cymarin, showing that splitting of the sugar, cymarose, results in reduction of action.

Oxidation of the aldehyde group on C₁₀ of strophanthidin to form strophanthidinic acid is followed by substantial diminution of action—approximately eight times less active in cats, and 153 times less active in frogs, than strophanthidin.

Saturation of the double bond in the side chain is accompanied by practically complete loss of activity as exemplified by dihydrostrophanthidin, dihydrostrophanthidinic acid, and isostrophanthidin. A residual effect may be sometimes demonstrated in sensitive animals, probably due to an intact lactone ring as in the case of dihydrostrophanthidinic acid.

The inertness of the sodium salt of saponified isostrophanthidin may be attributed chiefly to the disappearance of the double bond and lactone ring of the side chain.

Decrease or loss of action may be also suspected if the OH group on C₁₄ is reacted with another group in the molecule as in the case of pseudostrophanthidin, isostrophanthidin, and the sodium salt of saponified isostrophanthidin.

Very marked reduction or often complete loss of activity may occur when stereochemical rearrangement in the steroid ring system has taken place as illustrated by pseudostrophanthidin, allocymarin, allostrophanthidin, and presumably isostrophanthidin. These results indicate clearly that the digitalis-like action of strophanthidin and cymarin depends on not only a side chain with intact double bond and lactone ring, but also the steroid ring system in favorable spatial isomerism.

AUTHORS.

Allen, C. R., Stutzman, J. W., and Meek, W. J.: The Production of Ventricular Tachycardia by Adrenalin in Cyclopropane Anesthesia. Anesthesiology 1: 158, 1941.

At least one action of cyclopropane is to render the dog's heart more irritable to adrenalin by direct stimulation of a brain center above the pons which sends impulses to the heart by way of the sympathetic nerves. The direct action of adrenalin on the heart thus sensitized produces ventricular tachycardia.

AUTHORS.

Parker, Robert L.: Pulmonary Emphysema: A Study of Its Relation to the Heart and Pulmonary Arterial System. Ann. Int. Med. 14: 795, 1940.

An anatomic study was made of the heart and pulmonary arterial tree in thirty-two cases of essential emphysema. It was found the emphysema produced enlarge-

ment of the right ventricle in 75 per cent and resultant cardiac failure with decompensation in 44 per cent of the entire group. The severity of emphysema seemed to be closely correlated with the incidence of congestive heart failure as well as to the frequency and extent of right ventricular enlargement. Arteriosclerosis of the pulmonary arterial tree was noted to some degree in 80 per cent of the cases. Arteriosclerotic changes were noted most frequently in the arteries, and narrowing of the arteriolar bed was found in 66 per cent of the total cases studied. The degree of obliteration of the arteriolar bed seemed to be influenced by the severity of emphysema, yet there was no direct correlation between the degree of arteriolar sclerosis and the degree of right ventricular enlargement, nor any relationship between the extent of these pulmonary arteriolar changes and the extent of arteriosclerotic changes in the coronary arteries or the aorta. It was concluded, therefore, that the arteriosclerotic changes of the pulmonary vessels in emphysema represent secondary manifestations of an existent hypertension within the pulmonary circuit which probably is produced by obstruction in the capillary bed. Whereas it is reasonable to assume that when the degree of obstruction in the arteriolar system is great, there is an augmentation of the pulmonary hypertension, it is doubtful that the amount of pulmonary arteriosclerosis seen in the usual case of emphysema produces alone a very marked obstruction to the pulmonary circulation.

AUTHOR.

Smith, Lucian A., Allen, Edgar V., and Craig, Winchell McK.: Time Required for Blood to Flow From the Arm and From the Foot of Man to the Carotid Sinuses. I. Effect of Temperature, Exercise, Increased Intramuscular Tension, Elevation of Limbs and Sympathectomy. Arch. Surgery 41: 1366, 1940.

The mean circulation time from the arm to the carotid sinus of normal persons in the present study was twenty and one-tenth seconds. The range was twelve and four-tenths to thirty-three and two-tenths seconds. The mean circulation time from the foot to the carotid sinus was thirty-eight and seven-tenths seconds. The range was twenty-two to sixty-seven seconds.

The temperature of the skin of the extremities has a prominent effect on circulation time from the foot to the carotid sinus and from the arm to the carotid sinus. Warmth of the skin decreases the circulation time, and coldness of the skin increases it.

Exercise of the legs decreases circulation time in the legs.

Elevation of an extremity decreases circulation time in the extremities.

Lumbar sympathectomy decreases circulation time in the legs.

The increase of intramuscular tension caused by strychnine tends to decrease circulation time in the legs.

AUTHORS.

Lund, Curtis J.: The Recognition and Treatment of Fetal Heart Arrhythmias Due to Anoxia. Am. J. Obst. & Gynec. 40: 946, 1940.

Impending fetal asphyxia can be determined by careful frequent auscultation during active labor.

A method for continuous auscultation and recording of fetal heart sounds is described.

Fetal heart arrhythmia due to anoxia is described and the response to oxygen recorded.

The etiologic factors of fetal anoxia are discussed.

Early recognition of fetal anoxia and treatment by maternal oxygen therapy will prevent many cases of asphyxia neonatorum.

AUTHOR.

Cutts, Frank B., Clagett, A. Henry, Jr., and Fulton, Frank T.: Smallness or Absence of Initial Positive Deflections in the Precordial Electrocardiogram and Cardiac Infarction. A Study of Patients Who Came to Autopsy. Arch. Int. Med. 67: 509, 1941.

In routinely taken electrocardiograms the absence of the initial positive deflection in chest Lead IV F is evidence for the presence of cardiac infarction in the great majority of cases.

An abnormally small initial positive deflection in chest Lead IV F is associated with cardiac infarction in about one-half of the cases in which it is found.

A sharp distinction between abnormal and normal initial positive deflections is impossible in a few cases because of variations found in serial records.

A relatively small, grossly abnormal QRS complex in the precordial electrocardiogram may occur at times and is strong evidence for the presence of cardiac infarction.

In the presence of extreme cardiac enlargement or gross intrathoracic abnormality some caution is indicated in interpreting a small or absent initial positive deflection. An absent or abnormally small initial positive deflection in Lead IV F will rarely occur in the absence of either definite cardiac disease or significant extracardiac abnormality within the chest.

The presence of bundle branch block renders less reliable abnormality of the initial positive deflection or of the S-T interval in the precordial electrocardiogram.

In an interpretation of abnormalities in the initial positive deflection of the chest lead, the deviations of the S-T interval in Lead IV, the clinical history and findings, and the evidence provided by the limb leads should all be carefully considered in every case before a diagnosis is attempted.

AUTHORS.

Evans, Courtenay, and Bourne, Geoffrey: Electrocardiographic Changes After Anoxemia and Exercise in Angina of Effort. Brit. Heart J. 3: 69, 1941.

One-third of all cases with angina of effort show no changes in the four lead electrocardiograms.

Nearly half of this group with no cardiographic abnormality give changes suggestive of myocardial disease following anoxemia with 10 per cent oxygen for three to five minutes or after an exercise test.

The abnormal and normal response to anoxemia and exercise are described and discussed.

The exercise test gives an abnormal response slightly more often than the 10 per cent anoxemia test, but changes may occur after anoxemia when none follow after exercise.

AUTHORS.

Wood, Paul: Pulmonary Embolism: Diagnosis by Chest Lead Electrocardiography. Brit. Heart J. 3: 21, 1941.

Acute pulmonary embolism may be difficult to distinguish from posterior myocardial infarction, both clinically and by means of limb lead electrocardiograms.

Multiple chest lead cardiograms afford a good method of differential diagnosis.

In posterior myocardial infarction, as is well known, there may be no cardiographic change, or the RS-T segment may be depressed, or the T waves may be very tall.

In pulmonary embolism sufficient to cause right ventricular stress there is sharp inversion of the T wave, maximal and for the longest duration in the right pectoral lead; usually, but for a shorter duration, in the left pectoral lead; and rarely, and for the shortest duration, in Lead IV.

Similar changes may be found in all conditions giving rise to right ventricular stress.

AUTHOR.

Mortensen, Vagn: The QRS Complex in Precordial Leads in Anterior Wall Infarction. True and False Infarction Curves. Am. J. M. Sc. 201: 349, 1941.

In most clinical works the typical QRS changes in precordial leads in anterior wall infarction are described in terms indicating absence or marked diminution of the R wave; in addition atypical split or W-shaped QRS complexes have been described. The occurrence of a normal QRS complex in IV F in anterior wall infarction has been reported too.

This paper gives a preliminary report on the changes in the QRS complexes in precordial leads in twenty-three clinical cases of anterior wall infarction observed by the writer. In these cases 192 electrocardiograms were taken in the three conventional leads and in two precordial leads, CF₂ and IV F, from a few hours to several years after the acute injury. Twenty of the twenty-three cases showed an initial negative deflection in both CF₂ and IV F, and two other cases showed an initial negative deflection in either CF₂ or IV F in all the records. Therefore this abnormality must be looked upon as a very constant change in anterior wall infarction.

The QRS changes in precordial leads in anterior wall infarction are analyzed, and it is pointed out that these changes are far more characteristic than suggested by previous investigations. It must be considered erroneous to characterize the QRS changes in anterior wall infarction by absence of the R wave, as this explanation covers merely a minor part of the infarction curves (clear-cut central infarction curves), and it is sufficient to characterize the QRS changes in a good many cases, besides being directly misleading in some cases. On the other hand, practically all the QRS changes observed may be analyzed according to common simple rules under the supposition that anterior wall infarction implies two factors, (1) appearance of a Q wave and (2) diminution or complete disappearance of the R wave. The first of these factors is very constant, whereas the other is very variable, giving rise to the many variations in the features of the QRS complex.

The two ways in which a classical ("central") infarction curve may develop from a normal diphasic QRS complex are described (Fig. 2), and the conceptions "true infarction curve" and "false infarction curve" are introduced.

According to the writer's interpretation of the QRS changes in anterior wall infarction, a small initial R wave, which often is reckoned as equal to complete absence of the R wave in connection with anterior wall infarction, represents a considerable deviation from the typical changes. A small initial R wave in a presternal derivation is of no positive significance to the diagnosis of anterior wall infarction, as this abnormality is very common in marked preponderance of the left side of the heart.

The practical result of the view of the QRS changes in precordial leads in clinical cases of anterior wall infarction, as described here, will be that *particular attention must be paid to the presence of an initial negative deflection, with or without absence of the R wave, in the QRS complex in precordial leads.*

AUTHOR.

Blair, H. A., Wedd, A. M., and Young, A. C.: The Relation of the Q-T Interval to the Refractory Period, the Diastolic Interval, the Duration of Contraction, and the Rate of Beating in Heart Muscle. *Am. J. Physiol.* 132: 157, 1941.

In turtle heart strips the electrical activity is recorded from pairs of electrodes, one member of each pair being against the tissue and the other at a distance. The record permits the measurement of the interval between the depolarization and the repolarization of the tissue at a given region. This interval is called the Q-T interval. It is shown to coincide with the absolutely refractory period. It is shortened to one-half or less of its maximal value in a single very early beat. Further slow shortening occurs when the strip is driven for periods at a series of increasing rates. The lengthening of Q-T on slowing the rate is a slower process. Evidence is presented that repolarization arrests the contractile process in the muscle, leading to the conclusion that the electrical processes control the mechanical rather than the mechanical, the electrical. In this connection it is shown that the duration of contraction as measured, for example, from half contraction to half relaxation is related linearly to the Q-T interval over a wide range. In the human heart it is shown that in recovery from exercise there is no fixed relation between the Q-T interval and the rate.

AUTHORS.

Eppinger, Eugene C., Burwell, C. Sidney, and Gross, Robert E.: The Effects of the Patent Ductus Arteriosus on the Circulation. *J. Clin. Investigation* 20: 127, 1941.

Studies of the circulation made on six patients before and after surgical closure of an uncomplicated patent ductus arteriosus show that:

When the ductus arteriosus is open, the blood flow is from the aorta to the pulmonary artery.

There is no flow of blood from pulmonary artery to aorta. Therefore, these patients do not have arterial unsaturation and are not cyanotic.

The volume of blood flowing from aorta to pulmonary artery varied from 4 to 19 liters per minute, which is 45 to 75 per cent of all the blood pumped into the aorta by the left ventricle. These flows occurred in patients with large ducti and under temporary conditions which are known to elevate the output of the heart.

The left ventricle expelled from two to four times the volume of blood expelled by the right ventricle in a given period of time.

Adjustment of the circulation to the patent ductus may be made by an increase in the output of the left ventricle. If this is not sufficient to compensate completely for the leak through the ductus, there may be, in addition, a diminution in the blood flow to the periphery.

Comparable studies in dogs with an artificial aorta-pulmonary artery fistula showed similar circulatory adjustments.

Knowledge of the circulatory changes which occur with patency of the ductus permits a better understanding of the signs and symptoms associated with this condition. Furthermore, these studies of the circulation supply direct evidence of the beneficial effects of operative closure of the ductus in improving the peripheral circulation in some of the patients and in reducing the work of the heart in all of them.

AUTHORS.

Nichols, Charles F.: A Study of Syphilis of the Aorta and Aortic Valve Area. *Ann. Int. Med.* 14: 960, 1940.

A detailed study of seventy cases of syphilitic aortic insufficiency forms the basis of this report. In addition, the pathology of syphilitic aortitis, the diag-

nosis of uncomplicated syphilitic aortitis and an analysis of forty-one cases of syphilitic aortic incompetency which came to autopsy have been presented. Of the seventy cases in the series the ratio of males to females was 6 to 1. Fifty-three of the patients were colored; seventeen were white. The average age was 46.04, with extremes between 28 and 64. The average interval between primary infection and the onset of symptoms was twenty-two years. The most common presenting symptom was dyspnea on exertion, which occurred in 71 per cent. The rarity of paroxysmal dyspnea and pain was noted. An increase in the size of the heart was noted in 93 per cent. The average duration of symptoms before medical attention was sought was ten months, the shortest, two weeks, and the longest five years. Edema of the ankles was present in 40 per cent upon first admission to the hospital. The typical to-and-fro murmur of aortic insufficiency was present in 87 per cent. The presence of a loud musical diastolic murmur and thrill in five patients was discussed and its pathology explained. The average pulse pressure was 84 mm. of mercury. The Wassermann reaction was positive in 85 per cent of the patients. In addition, the appearance on fluoroscopic examination was discussed, and the absence of any noteworthy features in the electrocardiogram stressed. The differential diagnosis between syphilis, rheumatism, hypertension, and atheroma of the aortic valve was considered. The salient points in the clinical course of the disease were discussed, and a possible explanation suggested for the rapid myocardial breakdown.

AUTHOR.

Loewenberg, Samuel A.: A Valuable Sign in the Diagnosis of Functional Aortic Insufficiency. *Ann. Int. Med.* 14: 991, 1940.

In functional aortic insufficiency the systolic pressures in the upper and lower extremities are about equal. In organic aortic insufficiency the systolic pressure in the lower extremity is from 50 to 100 or more mm. of mercury higher than in the upper extremity.

AUTHOR.

Walsh, Bernard J., and Sprague, Howard B.: The Treatment of Congestive Failure in Children With Active Rheumatic Fever. *J. A. M. A.* 116: 560, 1941.

Forty-four children with congestive failure during active rheumatic fever were given various drugs (theobromine calcium-salicylate, theobromine sodium-acetate, theobromine sodium-salicylate, mercupurin, salyrgan and digitalis) for their effect on the heart and circulation.

The xanthine diuretics were found to be of greatest value, in particular theobromine calcium-salicylate or theobromine sodium-acetate in the dose of 1 Gm. three times a day. Theobromine sodium-salicylate given by mouth was found less effective but was useful when given rectally.

Mercurial diuretics given intravenously are effective in producing diuresis but should not be given immediately after full digitalization because of the danger of inducing toxic digitalis reactions during the loss of fluid.

Digitalis proved to be of value, but it was found necessary to use great care in its administration.

AUTHORS.

Perry, C. Bruce: Rheumatic Heart Disease in Identical Twins. *Arch. Dis. Childhood* 15: 177, 1940.

Two pairs of apparently identical twins are described. In the first both children suffered a similar rheumatic attack following a sore throat, which in one only produced scarlet fever. In the second, one child only developed acute

rheumatism and carditis although they had been brought up together. It is concluded that while heredity is of considerable importance in the causation of acute rheumatism, another factor, probably infection, plays an equally, if not more, important role.

AUTHOR.

Thomas, Caroline Bedell, France, Richard, and Reichsman, Franjo: The Prophylactic Use of Sulfanilamide in Patients Susceptible to Rheumatic Fever. J. A. M. A. 116: 551, 1941.

Sulfanilamide was given continuously to fifty-five patients with a recent history of acute rheumatic fever during seventy-nine person-seasons between 1936 and 1940. Sixty-seven patients with similar history, who were given no prophylactic treatment, were observed simultaneously during 150 person-seasons.

The drug was taken from November through June, usually in a dose of 1.2 Gm. daily.

No serious toxic effects were observed. Mild cutaneous eruptions and some drop in total white blood cell count without granulocytopenia occurred in a few patients. The leucopenia was self-limited in duration and was of no apparent clinical significance.

Pharyngeal cultures positive for the beta hemolytic streptococcus were less numerous and showed a lower percentage of the organisms among treated patients than among control patients.

While taking sulfanilamide, none of the patients had a major attack of acute rheumatic fever or an acute beta hemolytic streptococcus infection.

Fifteen major attacks of acute rheumatic fever developed among patients not taking sulfanilamide during the control period. One patient, treated during the winter months, had an acute rheumatic recrudescence in August when he was not taking the drug. Five control patients suffered from acute illnesses which might have been of rheumatic character. One control patient was hospitalized with an acute beta hemolytic streptococcus infection.

Subacute bacterial endocarditis developed in two control patients.

Four deaths occurred among the control group, one from acute rheumatic fever and two from subacute bacterial endocarditis. The cause of death in the other case is uncertain. There were no deaths among persons in the treated group.

Sulfanilamide may safely be administered in small daily doses over a long period of time. It appears to be of value in preventing recrudescences of acute rheumatic fever.

AUTHORS.

Seegal, David, and Earle, David P., Jr.: A Consideration of Certain Biologic Differences Between Glomerulonephritis and Rheumatic Fever. Am. J. Med. Sc. 201: 528, 1941.

A limited consideration of certain biologic differences between acute glomerulonephritis, chronic glomerulonephritis, and rheumatic fever indicates that:

Although both diseases appear to be initiated by Group A hemolytic streptococcus infection, the geographic incidence of acute glomerulonephritis is similar for all latitude regions in North America, whereas the incidence of rheumatic fever is less frequent in the southern than in the northern latitude regions of North America.

Although twice as many males as females contract glomerulonephritis, this sex variation is not apparent in rheumatic fever.

The preceding clinical infection in acute glomerulonephritis is a "deep" hemolytic streptococcus infection in at least two-thirds of the cases, in contrast to the usual superficial pharyngitis preceding the onset of rheumatic fever.

There is a distinct shortening of the latent period following infection in the exacerbation of chronic nephritis as compared with that in acute glomerulonephritis. This shortening of the latent period in exacerbation or relapse is absent in rheumatic fever.

Relapse, while a rarity following the healed state of acute glomerulonephritis, is a common if not regular occurrence following the rheumatic episode.

AUTHORS.

Farquhar, Lucille R., and Paul, John R.: Rheumatic Fever in New Haven, Conn. A Survey of Recent Hospital Admissions. Public Health Reports 55: 1903, 1940.

Data relative to rheumatic fever have been collected from all of the three general hospitals in the city of New Haven, Conn., and from these data estimates have been made on the annual number of active and inactive cases of rheumatic fever admitted to these institutions.

The average number of hospitalized cases of active rheumatic fever in the city of New Haven is 40 per year (an annual case rate of 29 per 100,000).

The active cases make up 1.2 per cent of the admissions to the medical services of local hospitals, and the inactive rheumatic heart disease cases make up an additional 1.5 per cent of these admissions.

From the standpoint of total admissions to the medical service of the New Haven Hospital this disease occupies a position of numerical importance which is greater than that of other acute infectious diseases, such as poliomyelitis, scarlet fever, measles, pertussis, and diphtheria, but less than that of the two major chronic infectious diseases, tuberculosis and syphilis.

We now have two rough measures of the prevalence and of the severity of this disease in this community. Their relative significance can be best appreciated when comparisons are eventually available from other localities.

AUTHORS.

Sheehan, H. L., and Sutherland, A. M.: The Pathology of Heart Disease in Pregnancy. J. Obst. & Gynaec. Brit. Emp. 47: 597, 1940.

An analysis was made of the clinical and pathologic findings in 108 obstetric patients who showed acute or chronic lesions of the heart valves at autopsy. For purposes of control these were compared with the autopsy findings in 215 women of child-bearing age who were not pregnant and who had similar valve lesions, and in 705 obstetric patients with normal valves. The following conclusions were drawn:

Chronic rheumatic valvular disease is present in 1.5 per cent of all obstetric patients in this locality. The mitral and aortic valves are involved with about the same frequency as in women not pregnant, but tricuspid lesions are found at autopsy much less commonly than in women not pregnant. The clinical diagnosis of particular chronic valve lesions is much better when heart symptoms are present than when they are not present, but a correct diagnosis is made in less than half of the cases. The difficulties in clinical diagnosis make it impossible to place full reliance on studies based on clinical data alone.

The mortality in women with chronic valve lesions was 6.3 per cent; 0.9 being due to superimposed ulcerative endocarditis, 2.9 per cent to other cardiac causes, and 2.5 per cent to noncardiac complications.

Nearly half the patients had had some evidence of congestive failure which usually began either in the first few weeks of pregnancy or at about six months. This was related to the type of valve lesion, severe mitral stenosis and mitral stenosis combined with aortic stenosis being the most serious, while incompetence of valves

was of less significance. The degree of hypertrophy of the heart did not appear to be a factor of importance in causing decompensation.

Deaths during or immediately after labor are usually not due to the progressive exhaustion of a badly decompensated heart, but are in most cases catastrophic acute heart failures in patients who have been either not or only slightly decompensated. Such acute heart failures are not satisfactorily described as acute pulmonary edema, because the lungs are edematous at autopsy in nearly all patients suffering from heart disease, whatever the manner of death.

The deaths during pregnancy or the late puerperium are several times as common as in patients not pregnant.

While many patients have never had congestive failure before, any patient whose heart becomes decompensated in a pregnancy will almost inevitably have the same condition in every subsequent pregnancy.

The American Heart Association Classification is of some value when it is based on the patient's condition in the last quarter of pregnancy, but it is not of help in assessing the prognosis before this stage of pregnancy.

The common belief that decompensation of the heart is related to a myocarditis or acute pancarditis does not rest on a satisfactory basis. On the other hand, simple recurrent endocarditis superimposed on old chronic valve lesions shows a very much higher incidence in pregnant women than in those not pregnant, and in those whose heart is decompensated than in those in whom it is not. The reason for the very high incidence in obstetric cases is not clear, but the recurrence appears to develop in the course of pregnancy and not in the puerperium. Recurrent endocarditis cannot be diagnosed satisfactorily during life except by inference. Though its exact significance remains to be established, it is an important complication of chronic valve lesions.

Simple acute endocarditis occurs in pregnancy with about the same frequency as in women not pregnant, and does not present any special features.

Ulcerative endocarditis superimposed on old chronic valve lesions and subacute bacterial endocarditis are rather commoner in pregnant women than in those not pregnant. These conditions develop during the course of pregnancy and not in the puerperium. They may be based on recurrent endocarditis. They lead to a particularly severe type of decompensation.

Primary ulcerative endocarditis (without previous chronic valve lesion) is very much less common in pregnant women than in women not pregnant. It appears from the literature that an ulcerative endocarditis developing in the puerperium was very common in the preantiseptic days of obstetrics, but this type of valve lesion does not seem to occur nowadays.

A patient who has any kind of valve lesion, chronic, recurrent, acute, or ulcerative, may also have pyelonephritis, hypertensive toxemia, eclampsia, or puerperal sepsis, but these diseases do not have any relation to the valve lesion, either as cause or effect.

Deaths associated with congenital heart disease, cardiac neurosis, or syphilis or primary sclerosis of the aortic valve are rare.

AUTHORS.

Robinson, Samuel C.: Hypertension in Relation to Height. *J. Lab. & Clin. Med.* 26: 930, 1941.

A gross anthropologic study of 2,552 men and 2,021 women shows for the first time in medical literature the positive correlation of height to blood pressure. Blood pressure is shown in this study to be affected by height. A review of the literature shows that no study, thus far, has found the height difference as reported in this paper. An explanation for this failure is probably due to a lack of correct

statistical delineation of build types and the exclusive reliance upon mean and modal pressures, instead of a study of the incidence of low and high pressure distribution and the actual to expected ratio.

The incidence of tall men and women decreased steadily with an increase in age. This is an unusual and striking phenomenon, and is probably due chiefly to a high mortality of tall persons in earlier age groups. In a random group of mixed builds and weights short men and women will show higher mean and modal systolic and diastolic blood pressures than tall men and women. Short men and women showed a higher incidence of high pressures than tall men and women. When the build groups are separated and held constant, a marked difference in blood pressure is noted between tall and short persons and is reversed to the height relationship mentioned above. The tall lateral or broad person is more susceptible to hypertension than the short lateral one and is less likely to have a low pressure. Tall lateral or broad men show an actual to expected ratio of about two and one-half times as many systolic and diastolic hypertensives as short lateral men. Tall lateral women show twice as many systolic and diastolic hypertensives as short lateral women. Tall lateral women show less than one-third the low systolic and diastolic pressures as short lateral women. Tall lateral men have a slightly smaller incidence of low pressure than short lateral men. The actual to expected ratio shows that among linear or thin men the tall men have only one-half as many low systolic and diastolic pressures as the short men. The actual to expected ratio shows no difference between the short and tall linear or thin women of low and high pressures.

In a previous paper it was shown that the lateral or broad build person in any height group carried the highest incidence of hypertension. In this paper it is shown that lateral build is most often found among short men and women. This unequal distribution of lateral build in short and tall persons explains the discrepancy mentioned. Although the tall person carries a greater hazard of hypertension than any other person, the larger number of lateral builds among short persons causes the bulk of the hypertensive population to be found among short persons. The short person shows a higher incidence of hypertension than the tall one in any weight group. There are, therefore, three influencing height factors in hypertension. First, there is the difference in blood pressure between tall and short persons in specific build groups. This is purely a height difference. Second, there is the difference in pressure between tall and short persons when weight is held constant. Third, there is the difference in pressure between short and tall persons in any total group in which build and weight are naturally mixed. The second and third height differences are dependent upon the build factor.

AUTHOR.

Master, Arthur M., Gubner, Richard, Dack, Simon, and Jaffe, Harry L.: Differentiation of Acute Coronary Insufficiency With Myocardial Infarctions From Coronary Occlusion. Arch. Int. Med. 67: 647, 1941.

A clinical and electrocardiographic study was made of forty-eight cases of acute coronary insufficiency, i.e., recent myomalacia without acute coronary occlusion.

The myomalacia following coronary insufficiency differs, as a rule, from that following coronary occlusion by its focal and disseminated character and its localization in the subendocardium and papillary muscles of the left ventricle.

Clinically, coronary insufficiency is usually associated with some factor which increases the work of the heart or diminishes the coronary flow, most often in a subject with antecedent cardiac enlargement and coronary sclerosis. The precipitating factors in the series studied included: heart failure; shock due to operation, pulmonary embolism, acute hemorrhage, and infection; marked tachycardia or bradycardia; acute anemia; aorta valve disease, and hypertensive crises.

The electrocardiogram of acute coronary insufficiency with infarction is characterized by the presence of a depressed RS-T segment and flattening or inversion of the T wave in two or more leads. The occurrence of an elevated RS-T segment or a Q wave, particularly in Lead I, is rare. The electrocardiogram thus differs from that of acute coronary occlusion in which the latter changes are common.

The presence of a depressed RS-T segment in acute coronary insufficiency is attributed to the subendocardial localization of the infarction.

AUTHORS.

Koucky, John J., Beck, William C., and Hoffman, John M.: Peripheral Arterial Embolism. *Am. J. Surg.* 50: 39, 1940.

Acute arterial embolism of the extremities is a complication of other disease. It therefore adds the mortality of the embolism to the mortality of the pre-existing lesion. Embolectomy should be carried out in favorable cases, within six hours of the onset. Conservative measures may be of benefit and may save the extremity as there is a diffuse vasospasm accompanying the lodgment of the embolus. Amputation must, however, be done in a large percentage of the cases.

There is a "time of election" for the amputation, viz., when the patient's general status has been improved, and before the toxemia has developed. An amputation which does not open up new fascial spaces is one of choice.

AUTHORS.

Blumgart, Herrman L., Schlesinger, Monroe J., and Zoll, Paul M.: Angina Pectoris, Coronary Failure and Acute Myocardial Infarction. *J. A. M. A.* 116: 91, 1941.

A detailed clinical and pathologic study of 355 consecutive cases examined post mortem has been made with particular reference to the role of coronary occlusions and the collateral circulation in angina pectoris, coronary failure, and acute myocardial infarction.

In normal hearts intercoronary anastomoses larger than 40 microns are generally absent. Fine communications measuring less than 40 microns in diameter can be demonstrated by the injection of watery solutions but are probably of little functional significance in obviating the untoward effects of sudden coronary narrowing or occlusion.

Complete occlusion or considerable narrowing of one or more coronary arteries may exist without giving rise to any clinical signs or symptoms and without having produced myocardial damage.

The apparent inconsistency between the presence of long standing obstructive arterial lesions and the absence of significant pathologic or clinical evidence of myocardial damage was dispelled by the demonstration of a collateral circulation which served as a bypass in relation to the obstruction in each of these hearts.

Every patient suffering primarily from angina pectoris without evidence of valvular disease or arterial hypertension has shown old complete occlusion of at least one major coronary artery at post-mortem examination; in the majority of instances at least two of the three main coronary arteries had been occluded before the terminal illness.

Attacks of cardiac pain more prolonged than those of angina pectoris but unattended by evidence of myocardial infarction are more accurately described as attacks of coronary failure.

A comparative study of the clinical characteristics of coronary thrombosis and those of myocardial infarction forces the conclusion that coronary thrombosis and occlusion, per se, do not necessarily produce any characteristic clinical manifestations.

The syndrome usually called "coronary occlusion," which consists of prolonged substernal oppression or pain, a fall in blood pressure, pallor and the other manifestations of shock, and is accompanied by electrocardiographic changes, fever, leucocytosis and an increased sedimentation rate, in reality signifies myocardial infarction and should be so termed.

In all three of the discussed syndromes, i.e., angina pectoris, coronary failure and acute myocardial infarction, the underlying mechanism seems to be a relative disproportion between the requirements of the heart for blood and the supply through the coronary arteries. The changes in the myocardium resulting from this disproportion depend solely on the extent and duration of the relative ischemia, not on the manner in which they are produced.

The absolute necessity for immediate and complete bed rest, sedation, reduction of excessively high cardiac rates, and other measures designed to reduce the work of the heart in the presence of prolonged cardiac pain is emphasized as a means of limiting the extent of myocardial necrosis or even preventing its development. Such a regimen also affords an opportunity for the development of a more adequate collateral circulation.

AUTHORS.

Gouley, Benjamin A., and Anderson, Edward: Chronic Dissecting Aneurysm of the Aorta, Simulating Syphilitic Cardiovascular Disease; Notes on the Associated Aortic Murmurs. *Ann. Int. Med.* 14: 978, 1940.

Occasional cases of dissecting aortic aneurysm of the chronic type closely simulate luetic cardiovascular disease. Such patients present the signs of aortic valvular regurgitation and of aortitis. Progressive cardiac decompensation may continue for many months or even years. There is often no pain and no history of a painful attack, so that if it had been present it was relatively slight and soon forgotten. Life is terminated by heart failure, or occasionally by a long delayed secondary aortic rupture.

The aortic valvular leakage is directly dependent on the proximity of the dissection to the valvular ring. The dilatation of the latter and of the ascending arch of the aorta in the chronic cases suggests a loss of tonus possibly secondary to the destruction of some controlling mechanism. A "mechanical" noninfectious deformity of the aortic leaflets may result from long-continued inefficient closure of the aortic valve.

Notable clinical features were: (1) the persistently negative serologic tests for syphilis in the large majority; (2) the usually marked and often enormous enlargement of the heart, especially of the left ventricle and the constant dilatation of the ascending arch of the aorta; (3) the relatively high incidence of hemoptysis in cases of chronic dissecting aneurysm showing signs of aortic regurgitation.

AUTHORS.

Whittenberger, James L., and Huggins, Charles: Ligation of the Inferior Vena Cava. *Arch. Surgery* 41: 1334, 1940.

Ligation of the vena cava above both renal veins causes death in dogs in a few hours from surgical shock due to accumulation of blood from two kidneys, in the posterior portion of the body. When oblique ligation of the vena cava between the kidneys is done, allowing development of collateral veins in one kidney, subsequent complete high ligation of the vena cava is well borne; it is not followed by shock or interference with renal function in the kidney with adequate venous drainage.

AUTHORS.

deTakáts, Géza, and Scupham, George W.: Revascularization of the Ischemic Kidney. Arch. Surgery 41: 1394, 1940.

Four hypertensive patients in whose cases the diagnosis of malignant nephrosclerosis was made were operated on with the idea that the ischemic kidney might obtain some additional circulation. The kidneys were decapsulated; the cortex was incised and the omentum or a pedicled muscle flap was wrapped around the kidney. The four case reports are summarized. One patient has been followed for three and one-half years. In no patient was there a definite improvement. It is possible that if patients with essential hypertension with earlier or more proximal vascular damage were subjected to such a procedure the condition might be arrested or improved. The importance of taking renal biopsy specimens and the difficult interpretation of biopsy observations in the early stages are emphasized. For the late stages in which the patient is referred to the surgeon, renal vascularization has been of no value.

AUTHORS.

Matas, Rudolph: Personal Experiences in Vascular Surgery. Ann. Surg. 112: 802, 1940.

In a historical preface the author traces in a most interesting way, the development of surgery of blood vessels, especially at the Charity Hospital in New Orleans. This is an interesting chapter in medical history. In regard to the author's personal experiences he states that, "my internship in a hospital where the surgery of the blood vessels had become a proud historic tradition, my association with the great surgeons and teachers just mentioned, who were especially concerned with the cure of aneurysm, and the anatomic experience that I had acquired early in my career as demonstrator of anatomy for over ten years in the dissecting rooms of the medical school, all combined to give me a special interest in vascular pathology and thereby to utilize the unusual opportunity given me to study, clinically and surgically, the ever fascinating problems that for practically 60 years have presented themselves to me as a visiting surgeon of the Charity Hospital and of the other local institutions with which I have been associated."

In a separate section the author describes briefly the development of his special operation "endo-aneurysmorrhaphy."

The larger portion of the paper is devoted to a classified summary of 620 operations upon the blood vessels performed for all causes between the years 1888 and 1940. This summary is in a statistical manner and describes first the anatomic distribution of the operations, second the regional classification in detail with results of the carotid vessels, and third a summary of procedures employed in the operations.

There is included a chronologic bibliography of contributions to vascular surgery by the author.

McCULLOCH.

Matas, Rudolph: Aneurysm of the Abdominal Aorta at Its Bifurcation into the Common Iliac Arteries. A Pictorial Supplement Illustrating the History of Corrine D., Previously Reported as the First Recorded Instance of Cure of an Aneurysm of the Abdominal Aorta by Ligation. Ann. Surg. 112: 909, 1940.

Among the more salient conclusions that may be drawn from the clinical and post-mortem studies of the case are:

The patient died 17 months and 9 days after the ligation of the abdominal aorta for a leaking (ruptured) syphilitic aneurysm of the abdominal aorta at the bifurcation, including both common iliac arteries.

The cause of death was tuberculosis—a cause unrelated to the aneurysm.

That the collateral circulation *above and below the aneurysm* was well established before the ligation of the aorta.

That the patient had been clinically cured of the aneurysm, and that this had ceased to be an active factor in her invalidism fully three months before her death.

The clinical evidence of cure was fully confirmed at the post mortem by the complete consolidation, contraction of sac contents, and beginning organization of the clot.

The invalidism and general disabilities, that hospitalized the patient until her death, were caused by the ravages of a disseminated widespread pulmonary, lymphatic, and joint tuberculosis, which flourished with unusual rapidity and luxuriance in a soil seemingly fertilized by a saturating and malignant luetic infection.

The aorta was totally occluded for 9 days following the ligation, during which all pulsation ceased and the peripheral pulses in the femoral and pedal arteries were suppressed.

During this period of total occlusion, the patient remained in a critical condition from threatened cardiac and pulmonary failure (passive congestion, patchy lobular pneumonia, pulmonary edema), which was relieved only by the yielding of the ligatures sufficiently to allow a small, reduced stream to flow through the ligated segment, thus converting a total atresia into a partial, stenotic occlusion.

The yielding or relaxation of the ligatures was not caused by any slipping of the knots, but as demonstrated at autopsy, by the soaking of the cotton fibers in the tissue juices, and the permeation and erosion of the fibers by giant foreign body cells.

The reduction of the aortic stream to about one-tenth or one-eighth of the caliber of the normal aorta was conducive to the final cure of the aneurysm by favoring a gradual deposition of clot and consolidation of the aneurysmal sac.

The anatomic and histologic studies of the aorta at the seat of the ligation showed, conclusively, that the cotton tape ligatures employed in this case (tightened without crushing force) were well tolerated by the tissues and caused no damage to the artery.

As shown in Figs. 7-11, the two one-half inch cotton tapes remained imbedded and incorporated in the aortic walls as a constricting ring for over 17 months without causing the slightest ulcerative, necrotic or thrombotic changes in the arterial coats and especially the intima which remained well-lined and polished with normal endothelium.

This experience shows that a partial occlusion can cure an aneurysm of the terminal aorta slowly, but with greater safety than an immediately total occlusion, without cutting through the artery or causing ulcerative alterations in the intima that might lead to hemorrhage or thrombosis.

It would seem that in large and leaking aortic aneurysms, with progressive subperitoneal extravasation, the collateral circulation is well established. In such cases the immediate total occlusion, which is especially indicated to stop leaking, may probably be better tolerated than in the earlier and nonleaking aneurysms, in which the collateral circulation has not had time to develop.

In view of the fact that sterile cotton tape is so well tolerated by the tissues and is ultimately incorporated by the aorta in the structure of its walls, it would seem unnecessary, and superfluous, to resort to extemporized autogenous fascial strips or to heterogeneous aponeurotic or other membranous strips, kept in stock, when the cotton tape will answer the same purpose with greater simplicity and safety.

Judging by the recent experimental evidence and the increasing number of clinical cures of aortic aneurysms by ligation and by suture methods, and the interesting evidence recently furnished by the laboratory, it would seem reasonable to expect that the great desideratum of abdominal aortic surgery, namely, the safe occlusion of

the aorta in any part of its abdominal and low thoracic course, by gradual methods of occlusion (Owings) will ultimately become as feasible and legitimate in the surgical clinic as in the experimental laboratory.

AUTHOR.

Behneman, H. M. F.: Should Coronary Disease and Hypertension be a Cause of Rejection in Industry? J. A. M. A. 116: 209, 1941.

Augmented work increases oxygen consumption. When the entire heart is confronted with a general lack of oxygen, the result is the picture of congestive failure; when there is a local lack of oxygen in the myocardium the result is angina pectoris, if mild, and infarction, if severe. The normal heart is usually able to meet the load placed on it by industry; there are a few exceptions. Persons with abnormal hearts, circulatory hypertension, and vascular diseases sometimes fulfill the demands made on them for a lifetime of activity but more often tend to fail eventually from even the routine activities and frequently fail when extraordinary activity is demanded. The presence of systemic disease is detrimental to normal circulatory function. Cardiac failure is in direct ratio to oxygen want. Exertion, disease, and emotional states cause hypertension, which is usually a forerunner of coronary disease. The mechanism of production of coronary disease and hypertension has been reviewed in the light of their relation to industry.

Industry should reject workers with coronary disease and hypertension only when the work contemplated is clearly destined to exceed their ability to respond normally. Industry should accept responsibility for the pathologic conditions it has created or exacerbated. Industry and unions should cooperate by allotting work within the ability of the worker with heart disease, because 70 per cent of those rejected are able to work at something. Differentiation between ordinary and extraordinary activity is difficult but possible.

In conclusion I offer the following thoughts toward solution of this controversial subject:

Institute pre-employment examinations with the right of the worker to sign a waiver which the law will recognize, thus acquainting the worker with his disabilities while protecting the employer.

In cases of questionable liability for cardiac disorders arising out of employment, demand careful medical analysis of each case by a competent examiner, who will painstakingly start his investigation not just from the time of onset of apparent disability but from a period many days previous thereto.

Establish wider use of electrocardiography, the value of which often exceeds that of the widely used roentgenography.

Amend the present industrial laws to allow finer gradations and degrees of incapacity.

Abolish the unfair laws extant in many states where a worker's death gives dependents full award when death has been due only to exacerbation of admitted, pre-existing disease. Industry should rightfully reject a claim for full death benefits in the rupturing of an old syphilitic aneurysm at work which would have ruptured soon without any exertion; at present there is little or no allocation of degree of responsibility. In California now the award is \$6,000 net.

Give the disabled worker prompt and proper medical care; rehabilitate him. Do not discard him, but develop him, and work with placement and rehabilitation bureaus which find work for disabled persons in skilled and unskilled labor.

Define more clearly in each state which occupational diseases are compensable and to what degree. As proposed by Robert T. Legge, create legislation enabling the person with heart disease to work under medical supervision yet releasing the employer and insurance carrier from financial liability in case of death.

At present, expert medical testimony is in a deplorable state. Create and define standards of qualification and urge their acceptance by commissions and courts.

Teach more industrial medicine in the nation's medical schools.

Create state medical boards of review which should decide which cases are worthy of consideration by commissions and courts. Such boards would eliminate many evils of the present system of decisions by lay referees, whose intentions are often buried in a mass of conflicting medical testimony.

Lastly, the principals must get together; the worker, the union, the employer, the insurer, and the physician all have something to learn from one another.

That is my answer to the question before me. It cannot be a sweeping, conclusive one because it depends on the merits of the worker in each individual case.

This answer is a challenge to the industrial physician, especially when, with the vast defense program of the United States imminent, there will soon be a chance to place every available person. It is one I know will be met successfully to provide another brilliant chapter in the annals of American medicine.

AUTHOR.

Murphy, Francis D., Correll, Howard, and Grill, John C.: The Effects of Intravenous Solutions on Patients With and Without Cardiovascular Defects. J. A. M. A. 116: 104, 1941.

No tests of cardiovascular function, so far known, will enable us to determine beforehand that the patient will respond unfavorably to fluids administered intravenously.

Careful clinical examination to determine the presence or absence of heart disease is still the best preventive for unfavorable reactions to fluid.

In the presence of heart disease, regardless of the state of compensation, fluids must be given slowly, in small volumes, preferably isotonic and repeated at intervals of not less than four to six hours.

These tests of cardiovascular function showed a few constant changes even with the precipitation of heart failure.

Fifty per cent dextrose solution, with or without 8 grains (0.5 Gm.) of aminophyllin, in volumes of 100 c.c. or more, at rates of 10 c.c. a minute, are extremely dangerous when used in treatment of heart failure, making from 50 to 100 per cent of the patients worse and precipitating failure in 20 per cent of grade 3 cardiac patients.

The danger of fluid injection in cardiac patients may not be in increasing blood volume per se but rather in further altering the already disturbed chemistry of the body fluid, thus increasing osmotic pressure derangements.

The ultimate fate and mode of distribution or loss of injected fluid is dependent on the kind and concentration of the solution, state of hydration of the patient, degree of cardiac compensation, level of venous pressure, and chemistry of body tissues influencing osmotic pressure.

Physiologic solution of sodium chloride may prove more useful in increasing blood volume than hypertonic solutions.

Noncardiac patients in the older age groups tolerated fluids as a substitution therapy, in amounts up to at least 3,000 c.c. daily in 1,000 c.c. doses at rates of from 20 to 40 c.c. per minute, even in the absence of dehydration.

Alteration of dextrose with the physiologic solution of sodium chloride obviated the changes in blood dilution, weight gain and occult or visible edema occurring with physiologic solution of sodium chloride alone.

The indiscriminate use of intravenous fluids, especially for persons with any cardiovascular defect, should be discouraged and the safeguards suggested be more strictly adhered to.

AUTHORS.

Morris, Noah, and Rogen, Alfred S.: Effect of Calcium on Diuresis in Cardiac Decompensation. *Lancet* 2: 545, 1940.

Calcium gluconate was administered intravenously to ten patients with cardiac edema. It had little immediate effect on the urinary output. In six out of seven patients who had previously been receiving digitalis the diuretic effect of this drug was increased when given after a course of injections of calcium gluconate. In nine out of ten patients with cardiac edema injections of parathyroid hormone enhanced the diuretic action of mersalyl and digitalis.

AUTHORS.

Cohen, Robert V., and Brodsky, Maurice L.: Allergy to Digitalis. *J. Allergy*. 12: 69, 1940.

The findings in a case of allergy to digitalis are reported. The patient exhibited the cardinal symptoms of an allergic drug response, i.e., fever, pruritus, urticaria, joint involvement, and edema of the face. Symptoms occurred only after the ingestion of the drug and were of short duration. During the days when the patient received no digitalis, there were no allergic manifestations. No other medication was taken during this period. When the digitalis was again administered the same symptoms reappeared. Since final cessation of digitalis administration, there have been no further allergic manifestations.

The negative skin tests obtained in this case are compatible with the diagnosis of digitalis allergy, since negative reactions are usually obtained in cases of drug allergy. The latter diagnosis depends largely upon the history, objective findings, and the results of the administration and withdrawal of the suspected agent. It is worthy of note that, following the first dose of digitalis, allergic manifestations appeared within thirty minutes. The patient already had an allergy to digitalis, either natural, or acquired.

AUTHORS.

Book Reviews

CALIBRATED PHONOCARDIOGRAPHY AND ELECTROCARDIOGRAPHY. A CLINICAL-STATISTICAL STUDY OF NORMAL CHILDREN AND CHILDREN WITH CONGENITAL HEART DISEASE: By Edgar Mannheimer, M.D. *Acta Paediatrica*, Vol. XXVIII, Suppl. II, Stockholm, 1940, 287 pages, 59 illustrations.

The author of this monograph has attempted a very difficult piece of research. He has tried to analyze the complex noises produced by the heart in a fashion similar to spectroscopic analysis of light, and to discover the energy recorded in six frequency bands, namely, below 100 cycles per second, 50 to 175 cycles, 100 to 250 cycles, 175 to 400 cycles, 250 to 500 cycles, and 500 to 1,000 cycles. This he has studied in 135 normal children from infancy to the age of 14 years, and in ninety children with congenital heart disease from "0 years of age to puberty." These groups were also investigated electrocardiographically.

Sound and electrocardiographic tracings were obtained with a complicated phonocardiograph which permitted simultaneous recording of the heart sounds and electrocardiogram. No simultaneous sphygmographic tracings were made; this imposes a serious limitation to the analysis of diastolic phenomena. Filters were introduced to permit the passage of the frequency bands mentioned and thus produce a crude sound spectrum. Energy, as recorded by the amplitude of the waves, was calibrated against vibrations produced by constant frequency oscillators of known voltage whose frequencies were 70, 175, 275, 375, and 700 cycles per second. An extensive review of the literature precedes the experimental work and should be useful for reference, for the bibliography contains 192 titles.

There are four divisions of the study, namely, (1) heart sound records of normal children, (2) electrocardiograms of normal children, (3) heart sound records of children with congenital heart disease, and (4) electrocardiograms of children with congenital heart disease. Brief comment may be made concerning each group.

1. *Heart Sound Records of 135 Normal Children.*—An effort was made to exclude all children with cardiac lesions or with a history of rheumatic infection. The first, second, and third sounds and auricular sounds and murmurs were analyzed as to frequency, amplitude, duration, and relation to the electrocardiogram. In this, as in the rest of the studies, the statistics were submitted to the most minute mathematical analysis—a refinement which impresses the reviewer as not fully justified by the data, largely because of the variables introduced by differences in chest wall thickness and resonance, and inevitable variations in microphone application pressure. The author found that these factors were pronounced in the lowest frequency ranges, which, of course, have the greatest energy components. He confirms the work of others in finding "that the heart sounds are, throughout, characterized by big, irregular vibrations of a high amplitude and a low frequency." A systolic murmur was recorded in three-fourths of these normal subjects. The dilemma of investigators of this phenomenon appears in this sentence: "Even when the amplitude of the murmur has been given as naught, a certain suggestion of rippling, has, as a rule, been noticeable during systole." To the reviewer, this suggests the inadvisability of using the term "murmur" to include inaudible vibrations, and the author found that this systolic "murmur" was, as a rule, imperceptible to auscultation. This does not, however, disprove the fact that normal ventricular systole is accompanied by inaudible and, at times, audible vibra-

tions. "Still, on examination, it is found that no significant difference exists as to frequency and amplitude between perceptible and imperceptible murmurs." The subjects were examined at the base and apex of the heart, erect and supine, and before and after exertion. The amplitude of the first heart sound was higher in the erect position and after work. A third heart sound was recorded in about 70 per cent of the cases, and in six of seventeen infants under 1 year of age. The auricular sound was found in 50 per cent of the cases; it had a fundamental frequency of about thirty, and was not heard on auscultation because of the absence of overtones.

2. *Electrocardiograms of Normal Children.*—One hundred eighteen subjects, between the ages of 2 and 14 years, were studied. Great variations were found, and the means of the figures were not significant. The mean of the P-R interval was 0.15 second, but he regards conduction as abnormal only when the time is in the neighborhood of 0.20 second. Sex differences found by others were not confirmed nor considered statistically significant. Not rarely, Q_s had an amplitude exceeding 25 per cent of the maximum QRS amplitude. The Q waves in Leads I and III decrease through childhood; they are greatest at the age of 3 years. T_s was negative in 19.5 per cent. A tendency to right axis deviation was found between 3 and 13 years of age, and right axis deviation should not be considered pathologic below 110 to 120 degrees. The amplitude of the chest lead is higher in children and decreases with age.

3. *Heart Sound Records of Children With Congenital Heart Disease.*—Although a large amount of data has been collected in this study of ninety patients, its value is questionable. This is largely because the author was obliged to forego any attempt to diagnose the specific defect, except in six autopsy cases. Of the whole group, twelve were cyanotic and sixty-eight were not. Records appeared to show that the first heart sound had a larger than normal amplitude within the frequency bands of under 100 cycles, and between 50 and 175 cycles. The second heart sound also showed a larger amplitude. The third heart sound was less common than in normal persons, but the auricular sound showed no significant average difference from normal. The systolic murmur was larger in amplitude. In the band of 50 to 500 cycles this murmur was recorded in 90 per cent of the cases and appeared to have a higher pitch than the normal systolic murmur. Ten patients had the continuous murmur of patent ductus arteriosus. In most cases it was of high amplitude.

4. *The Electrocardiograms of Children With Congenital Heart Disease.*—One hundred thirty-five patients, from birth to puberty, were included. Twenty-five were studied post mortem; fifteen were cyanotic, and ten were not. The conclusion is reached that "generally speaking, special diagnosis cannot in the individual case be based on the electrocardiogram." He confirms a previous observation of Seham that the form of the electrocardiogram is not always consistent with what is found at autopsy, especially with reference to axis deviation and ventricular hypertrophy. He suggests that this is to be explained as a result of conduction defects within the ventricles. In morbus caeruleus, large P waves and right axis deviation are the most important abnormalities. In noncyanotic patients the electrocardiogram is not rarely perfectly normal. Atypical, diphasic QRS complexes are the most characteristic changes. In certain cases, high amplitude of the QRS, with right or left axis deviation, may be found. In contrast with the electrocardiogram in acquired heart disease, that in congenital heart disease retains a consistent pattern when repeated on the same child. Exceptions to this are found in infancy.

In comparing auscultation with phonocardiographic records, the author found twenty-three tracings outside the normal as regards the four heart sounds, and only one of these was considered abnormal with the stethoscope; it was an accen-

tuated first sound. The second sound was considered accentuated on auscultation in thirty-two cases, whereas the sound tracing recorded only eleven. No gallop rhythms were diagnosed clinically, but the sound record was regarded as showing a few with pathologically increased third sounds and auricular sounds.

The reviewer agrees with the author that "future experience will decide the utility of the method with regard to cases of suspected congenital or acquired heart disease." The problem of calibrating heart sounds and murmurs in an objective manner has appealed, no doubt, to most workers in the field, but this solution assumes that such phenomena, as recorded from the chest wall, have a validity, and a relation to the same vibrations in the heart, which do not exist in such a simple quantitative ratio. Mannheimer's figures seem to show that a thick chest wall or breast tissue reduces the amplitude only in the lower frequency ranges, but so does firmer application of the chest piece, by altering the natural period of the skin diaphragm bounded by it. It is hard to reproduce sound records identically, even in the same person on successive trials.

The technical design of the instrument is excellent. However, arbitrary division of the recording into the frequency bands studied introduces a spurious simplification into a very intricate problem, a problem which can only be solved eventually by division into much narrower frequency ranges, thus giving records susceptible of harmonic analysis.

This monograph should, however, help to remove some of the misconceptions about the role of heart sound records and also to clarify the confusion in the minds of some concerning intensity of sound (which is being measured) and loudness, which is a subjective sensation. In graphic records we are searching for objectivity, and what we see in a sound tracing cannot reproduce what we hear, although this can be approached by logarithmic recording.

We need more of Mannheimer's type of work, even though his goal may not be attainable, nor, at the moment, have any practical significance. To the reviewer, the recording of a sound spectrum appears more likely to be of importance as a qualitative rather than a quantitative measure. Undoubtedly, the rapid refinement of electrical methods will give us increasingly valuable information.

HOWARD B. SPRAGUE.

ELECTROCARDIOGRAPHY IN PRACTICE: By Ashton Graybiel, M.D., Instructor in Medicine, Harvard Medical School, and Paul D. White, M.D., Lecturer in Medicine, Harvard Medical School. W. B. Saunders Co., Philadelphia, 1941, 319 pages, 272 illustrations, \$6.00.

All who, for the first time, have read a textbook on clinical electrocardiography, or who have taken a course in this subject, have felt the need for a large collection of records abundantly illustrating both the more common and the rarer deviations from the normal. Such a collection of records can be studied at leisure for practice in electrocardiographic interpretation, and may be used as a sort of pictorial encyclopedia when abnormalities of an unfamiliar kind are encountered. This work, in which some 270 electrocardiograms of all varieties are reproduced, meets this need in an entirely satisfactory manner. All of the tracings are beautifully reproduced, and, in all except a few instances, Lead IV F, taken according to the recommendations of the Committee on Precordial Leads of the American Heart Association, is reproduced below the three standard limb leads. The first 140 records are arranged according to diagnosis; the last 130, which are intended for practice in interpretation, are in random order. An excellent analytic index is supplied.

The reviewer does not hesitate to recommend this work in the highest terms to those who wish to increase their ability to interpret clinical electrocardiograms.

That he should agree wholly with every view expressed, or with the interpretation of all of the records reproduced, is hardly to be expected. Our knowledge of electrocardiography is not only far from complete; it is in rapid and vigorous growth. Under these circumstances a difference of opinion on many points is desirable and inescapable. Space is not available for detailed consideration of a number of electrocardiograms which, in the opinion of the writer, are wrongly interpreted, or show important features which are not mentioned in the text. In the way of general criticism the following comments are offered.

In the preface it is stated that clinical electrocardiography is an empirical science, and that it has developed by the careful study of records obtained in various types and stages of cardiovascular disease. This is emphatically not the case; if the knowledge gained from the very beginning, long before Einthoven to the present, by experiment, guided by well-conceived hypothesis, were taken away, there would be precious little left, either of the background or of the foreground of the subject.

The description and interpretation of each of the records reproduced is preceded by a brief but excellent summary of the relevant clinical data. The addition of this material is to be highly commended. It emphasizes the importance of considering the patient's history, the physical signs, and the laboratory data, including the electrocardiogram, together, instead of depending on any one of these alone. Unfortunately, however, Graybiel and White do not always make clear to what extent the conclusions which appear at the end of their discussion are based mainly upon the clinical data, and to what extent these conclusions are based upon the electrocardiographic observations. This may have the unfortunate result of encouraging the inexperienced to read far more into the electrocardiogram than can possibly be justified. It is often possible to make the diagnosis of myocardial infarction from the electrocardiogram alone, and tracings taken during an attack of angina pectoris may show changes characteristic of transient myocardial ischemia, but apart from these conditions the reviewer does not believe that "coronary disease" produces any electrocardiographic abnormalities that can be considered characteristic. It would be better if this term were never used under any circumstances in connection with the interpretation of the electrocardiogram.

FRANK N. WILSON.

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To coordinate and distribute pertinent information, a central office is maintained, and from it issues an ever widening stream of books, pamphlets, charts, posters, films, and slides. These activities all concern the recognition, prevention or treatment of the leading cause of death in the United States, diseases of the heart. The AMERICAN HEART JOURNAL is under the editorial supervision of the Association.

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JUL 33 1941

The American Heart Journal

A Journal for the Study of the Circulation

Published Monthly Under the Editorial Direction of The American
Heart Association

Vol. 21

JUNE



1941

No. 6

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PUBLISHED BY THE C. V. MOSBY COMPANY, 3525 PINE BOULEVARD, ST. LOUIS

Issued monthly. Subscriptions may begin at any time.

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